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THE PRESENCE OF LEPTOSPIROSIS OF A MILD TYPE (SEVEN-DAY FEVER) IN QUEENSLAND.

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FOREWORD.

(SIR RAPHAEL CILENTO.)

THE interesting work of Dr. Clayton and Dr. Derrick advances a step further the elucidation of the "undifferentiated short-period fevers" of Queensland. As early as 1907 a serious outbreak of what was at first thought, by its severity and by its gland involvements, to be a bubonic plague was observed at Mossman, in North Queensland, and cases recurred for about five years. The death rate was about 1%. The cases were described in detail in annual reports of this department. Dr. Smithson, the late Dr. P. S. Clarke, and later Dr. A. Breinl carefully investigated the available material. Dr. Breinl was at that time Director of the Australian Institute of Tropical Medicine at Townsville, and when, in 1922, the writer succeeded to that position, the problem presented itself as one which amid much excellently investigated work had remained unsolved. The close similarity with the composite picture presented in the Malay States, where in 1920 and 1921 various ill-defined short-period fevers were under investigation, was at once apparent; but cases were rarely reported and isolated groups had, as Dr. Clayton points out at Pomona, sometimes the features of a leptospirosis, sometimes of a typhus of the endemic type. It will be recalled that Manson

in his textbook of 1917, included Mossman fever with the doubtful series that embraced "seven day's fever" and "pseudo-typhus of Deli (Sumatra)". In 1922, in a personal communication just prior to his death, he stated that he was intrigued by its similarity with the newly recorded work on the Eastern leptospiroses. Manson-Bahr, in the seventh edition of "Manson's Tropical Diseases", inclined to the belief that it might prove similar to, or identical with, Japanese river fever.

Both these conjectures are right. The various outbreaks of "fever" on the Queensland coast have obviously been of mixed origin. Leptospiroses of several varieties, and at least two, and possibly three, kinds of typhus are included.

In 1923 it was possible to identify on clinical grounds endemic typhus, and its widespread occurrence has since been amply confirmed by laboratory investigations.

Official representations through Dr. J. S. C. Elkington, then Director of the Division of Tropical Hygiene, to Dr. J. H. L. Cumpston, Commonwealth Director-General of Health, enabled an investigatory party to be in readiness constantly to proceed to the site of any outbreak, but, fortunately or unfortunately according to the viewpoint, no epidemic outbreak occurred in North Queensland for some years. The only opportunity was provided in the investigation of mouse-borne typhus near Toowoomba and Warwick by Dr. F. Wheatland in 1925.

Association with the problem of the local leptospiroses save in an administrative sense was restricted to inquiry into some half dozen vague occurrences of "cane fever", "scrub fever", or "coastal fever", which came to observation only when the victims were already recovering, but which were typical enough of the Malayan groups to be recorded as "seven day fever". Slight as was the attention these cases attracted, and lightly as they were regarded by the canecutters and scrubworkers affected, they were a common enough concomitant of their work to be recognized as associated with these occupations by those engaged in them. It has since been demonstrated that typhus and leptospirosis may coexist in the same gang and may be equally light in incidence. Last year, of five men in one gang, all ill simultaneously, one had leptospirosis with jaundice and four had rural typhus, the sufferer from leptospirosis being earliest convalescent. Of another series, one man with proved leptospirosis was ill only three days and refused to go to hospital. Most return to work within a few weeks, and the average duration of illness is ten to fifteen days. The cases indeed show the wide range of severity seen elsewhere and perhaps modified by vector, personal resistance or other factor.

The work of inquiry was interrupted from 1924 to 1928, the only addition being the recognition of a case of rat-bite fever in the Mandated Territory of New Guinea; but by the last mentioned year, Fletcher's classical work in Malaya had admirably described the conditions found also in Queensland and had indicated the probabilities of the picture.

In 1929 Dr. A. H. Baldwin, Acting Director of the Institute of Tropical Medicine, prepared at request an outline of probabilities in respect of the undifferentiated fevers of North Queensland, including leptospirosis, and this was circulated to various medical practitioners who were considered interested or strategically located, but at the end of that year the Institute itself was abolished. Between this date and the outbreak of leptospirosis in 1933 and 1934, some few significant occurrences had been observed, apart from the frequent sporadic cases of typhus fever that extend irregularly along the whole coast, and have been reported as "urban", "rural", and also mite-borne of the "Japanese river fever" type.

Thus near Tully, Dr. J. J. Spencer under instruction investigated a case that showed very significant *post mortem* appearances on guinea-pig inoculation; in Ingham, on a farm that has since been visited several times by severe leptospirosis, a man died from "yellow atrophy of the liver"; rumours were received that "cane fever" was more than usually severe; and "old hands" predicted a series of bad "fever seasons" because of the unduly heavy rainfalls of several successive years.

The vast invasion of rats into Ingham in 1933 and 1934 was associated with an outbreak in which the emphasis was definitely on the leptospiral rather than the typhus factor. The organism was discovered by Dr. W. C. Sawers and Dr. T. J. P. Cotter who, acting on official instructions from the head office of the Commonwealth Department of Health, immediately attacked the problem. Dr. Morrissey and Dr. Leckie had already diagnosed the disease clinically.

It was obvious to all familiar with the locality and aware of the probabilities of the epidemic that the disease was neither new nor typical of European strains, nor wholly "Weil's disease". It was significant that it was carried mainly not by imported rats, but was endemic among local forms, notably *Rattus culmorum*; it was soon obvious that the organism was not *Leptospira icterohæmorrhagiæ* of European varieties, but had closer affinities perhaps with Japanese and Malayan strains; it was apparent indeed that in that respect it was strictly not "Weil's disease" but "para-Weil's disease". Finally, apart from the cases of typhus associated, it was obvious that the patients were very variously affected (of a series of 80 of the Morrissey patients, not one was jaundiced), and that there were at least three and possibly five clinical variants, possibly differing widely in clinical and, more importantly, economic significance. What these variants are has been a matter of the greatest interest and the closest study in the Department of Health of this State for some twelve months, and the results already achieved bid fair to be of considerable value.

The typing of the organisms proceeds with constantly greater approach to finality in accuracy; and several associated disease conditions have been discovered and investigated both in men and in animals.

This latest contribution from Pomona comes as an interesting commentary on, and addition to, the knowledge derived from the fields 700 miles further north.

CLINICAL INVESTIGATION.

(G. E. B. CLAYTON.)

The patient J.H.G. was a dairy-farmer, aged twenty-seven years, residing about eleven miles from Pomona. He first felt ill on July 19, 1936, and consulted me on July 22, complaining of severe frontal headache, feverishness, nausea and a little vomiting, loss of energy, anorexia and constipation. There were pains in the back, shoulder muscles and legs, "like influenza pains" (as he described them).

On examination the patient looked tired and drowsy. The tongue was furred and the breath heavy. There was congestion of the eyes and photophobia. The temperature was 40° C. (104° F.). It continued high, varying between 38·3° C. (101° F.) in the mornings and 40° C. (104° F.) in the afternoons, until it ceased abruptly on July 27. The fever was therefore of eight days' duration. The pulse rate was comparatively slow—90 to 100 beats per minute. There was tenderness in the epigastrium. The urine was of the usual febrile type. There was no rash, no jaundice, no enlargement of liver or spleen.

The course of the disease did not vary until July 27, when all symptoms abated. Appetite returned within three to four days. He was in bed for about fourteen days altogether. The illness left him very weak, and he felt tired and languid for some time, with bouts of headache and constipation. He did not regain his usual health for about one month after the illness was over. Recovery was then absolute.

The treatment was along the usual lines—mostly symptomatic. It included close attention to the bowels, relief of headache with acetyl-salicylic acid combinations, frequent sponging, a light nourishing diet, absolute rest and quiet in a darkened room, and a potassium citrate and sodium salicylate mixture.

A sample of blood was taken on July 22 and forwarded to the Laboratory of Microbiology and Pathology, Queensland Health Department, Brisbane, and a second sample for the study of residual agglutination on September 29.

The source of this man's infection is problematical. He admits drinking creek water while working in timber for a couple of months prior to getting ill, cutting cow-cane (which he often chewed) twice a week over the same period, and working in a barn infested with rats and mice. The incubation period cannot be determined. There were prodromal symptoms, languor, tired aching feeling and mild headache for three or four days before the disease was established.

Cases of fever similar to this one have occurred fairly frequently in Pomona. At least thirty have come under notice in the last five years, and there have been others among patients who have not sought medical attention. The fever is in general of a seven-day type. Headache is a consistent feature and the most prominent subjective symptom. In all cases the patients show congestion of the conjunctivæ, and invariably complain of photophobia. Constipation is the rule, but some patients have diarrhœa with foul-smelling motions. Most patients have a mild albuminuria. In no case has jaundice been noticed. The pulse is always comparatively slow. Although all patients have been acutely ill, they have never occasioned anxiety as to prognosis, and have all made an uninterrupted recovery. Those more severely affected are generally weak and debilitated for a period of up to two months; with a milder attack they are fit again in about a month.

All the infections have occurred in men ranging in age from sixteen to forty years. The main incidence has been in the summer and early autumn, although there has been an occasional case at any period of the year. Nothing suggesting an epidemic has been noticed, but last year there were two instances in widely separated families of brothers who contracted the complaint within seven to fourteen days of each other.

Seven-day fever is a disease that has a wide geographical distribution, including Malaya, Dutch East Indies, China and Japan. Its clinical features as they appear in Japan are described by Ido, Ito and Wani[1] as follows:

> There prevails in the province of Fukuoka a disease known as nanukayami, or seven day fever, the symptoms of which are like those of atypical Weil's disease. The latter does not usually show any icterus. Seven day fever has a sudden onset with fever, languor, congestion of the conjunctivæ, muscle pain, disorders of digestion, and swelling of the lymphatic glands. Moreover, albuminuria and leukocytosis appear in the earlier stages. Subsequently clouding of the vitreous humor may arise. The disease does not prevail in the cities, e.g. Fukuoka, but is restricted to the country. It runs a short course and apparently causes no fatalities.

There is clearly a close similarity between this description and the Pomona picture. In reference to the clouding of the vitreous seen occasionally in the Japanese patients, it is of interest that one Pomona patient went practically blind for seven to ten days. This occurred during the convalescent period, seven to ten days after cessation of the fever. It was ascribed at the time to a marked secondary anæmia and treated accordingly. In two or three weeks his sight was again normal. Enlargement of the lymphatic glands has not been noticed, but has perhaps been overlooked.

Not all the "coastal fevers" of Pomona have been of a seven-day type. In 1931 and 1932 there were a number of cases in which the fever lasted about eleven days and terminated by a crisis, or at times a false crisis. In quite a few cases the temperature came down by lysis over a period of about three to four days. These cases were suggestive of Brill's disease, although no rash was noticed.

Pomona is a township situated 86 miles north of Brisbane by rail, and 12 miles in a direct line from the coast. It has an elevation of 283 feet above sea level, parts of the countryside being more low-lying. It is the centre of a dairying and banana-growing district. Most of the land is cleared, and there is little virgin scrub left. There is some timber getting, but most of the good timber is cut out. It is not a sugar district, but most farmers have a patch of cow-cane. The average annual rainfall in the town is 62·88 inches. The population of the district is about 5,800. The fever patients have nearly all come from a strip of country on the coastal side of Pomona. All of this is well watered, with running creeks. Parts are hilly, while other parts are low-lying and swampy.

LABORATORY INVESTIGATIONS.

(E. H. DERRICK.)

Leptospirosis (Seven-Day Fever) in Guinea-Pigs.

When the blood sample taken from J.H.G. on the fourth day of his illness was received in the laboratory, the serum was separated from the clot and tested for agglutination with various organisms: *Eberthella typhosa*, *Salmonella paratyphi*, *Salmonella schottmülleri*, *Salmonella hirschfeldii*, *Proteus X 19*, *Proteus XK* and *Brucella abortus*. None of these were agglutinated. The clot was then ground up and

injected into guinea-pig G.1. This animal, after an incubation period of seven days, underwent a fever of four days' duration with a maximum temperature of 41° C. (See Chart I.) During the

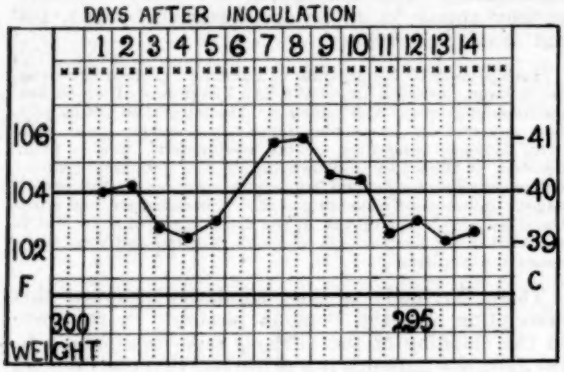

CHART I.
Temperature chart of guinea-pig G.1. Seven-day fever.

fever blood was obtained from it by heart puncture and injected into two more guinea-pigs, G.2 and G.3. Both of these also became febrile.

Guinea-pig G.3 was killed on the second day of fever, which was the fifth day after injection, and the organs were examined. The lungs contained numerous hæmorrhages varying in size from 0·05 to 0·3 inch across. There was a large hæmorrhage in the retroperitoneal tissues below the left kidney. There were no hæmorrhages seen elsewhere. The liver contained small yellowish-brown spots, presumably of necrosis. There was no jaundice. When an emulsion of the liver was examined by dark ground illumination leptospiræ were found, but were very scanty. Leptospiræ were successfully cultivated from the blood in Fletcher's and Schüffner's media.

Passage from guinea-pig to guinea-pig by blood or liver emulsion was continued for eleven generations.

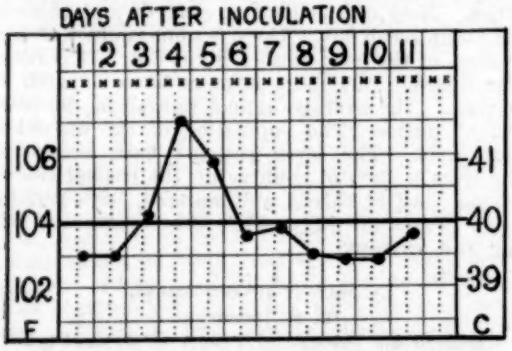

CHART II.
Temperature chart of guinea-pig G.6. Seven-day fever.

This ensured that the maximum virulence for guinea-pigs was attained. Of twenty-eight guinea-pigs infected, six were killed during the fever for investigation. Of the other twenty-two, only two died as a result of the leptospirosis. One of these was a young guinea-pig weighing 200 grammes, the other was an old one of 860 grammes. The animals that recovered were between 225 and 390 grammes in weight at the time of injection. Jaundice was not seen except in the two fatal cases.

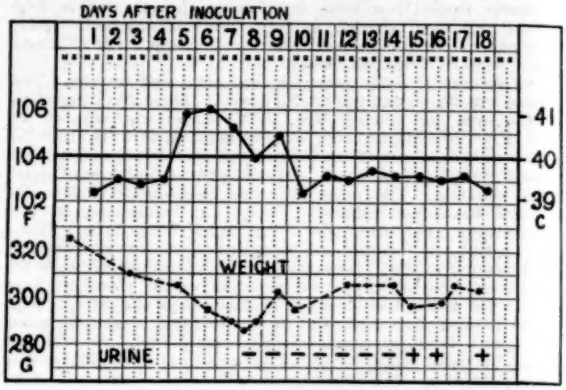

CHART III.
Temperature and weight chart of guinea-pig G.19. Seven-day fever. + means that leptospiræ were seen in the urine, – means that they were not seen.

The incubation period varied from two to eight days, with an average of 4·3 days. The duration of the fever in the non-fatal cases was from one to five days, with an average of 3·4 days. The temperatures reached from 40·4° C. to 41·7° C., with an average maximum of 41° C. (See Charts II and III.) The affected animal appeared ill for several days, eating little and sitting hunched up with staring fur. These features continued for a variable time after the temperature fell, gradually improving. A definite recurrence of fever has not been observed. Most guinea-pigs lost weight during the illness, some as much as 40 grammes. The weight was

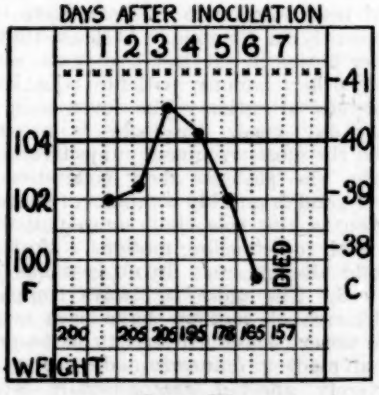

CHART IV.
Temperature chart of guinea-pig G.28. Fatal case of seven-day fever.

usually regained in a few weeks, but several have remained emaciated for months. Some guinea-pigs with milder attacks lost little or no weight.

In the two fatal cases the temperature rose on the second and third day respectively, remained elevated for two days, and then gradually fell, becoming subnormal. (See Chart IV.) Each became jaundiced

on the sixth day and, being moribund, was killed on the seventh. The smaller one dropped in weight from 200 to 157 grammes, the larger from 860 to 670 grammes.

The *post mortem* appearances of the six guinea-pigs killed at the height of the fever were in general similar to those of G.3 already described. Hæmorrhages were always present in the lungs, and occasionally also in the retroperitoneal tissues. Small yellowish points were usually present in the liver. The spleen was as a rule slightly enlarged. Jaundice was not seen. It was noteworthy how scanty were leptospiræ in the organs in the non-fatal cases during the fever. In each case a liver emulsion was examined by dark-ground illumination. Leptospiræ were found in only four of the six cases, and then only after much searching. In the other two cases they were not found at all, although reinoculation of liver in both instances reproduced the disease. Leptospiræ were not seen in the blood when it was examined directly with the dark ground, but were found in it in one of three cases in which double or triple centrifuging was employed.

With these six animals leptospiræ were not found by dark-ground examination in the kidney or other organs apart from the liver. Their absence from the kidney at this stage is in contrast to their abundance there later. In two guinea-pigs killed during convalescence, on the fifteenth and twenty-sixth days after inoculation, there was no difficulty in observing leptospiræ in the kidneys by dark-ground examination, or in reproducing the disease by reinoculation of kidney emulsion. No leptospiræ were found in the livers of these two guinea-pigs either with the dark ground or by reinoculation.

The *post mortem* appearances of the two guinea-pigs that died from leptospirosis were in general similar. There were in addition severe toxic spoiling of the organs and a generalized jaundice. Leptospiræ were seen by dark-ground examination in the blood, liver and kidney, there being one leptospira present in each one to six fields. Even in these fatal cases the leptospiræ were not nearly so numerous as in guinea-pigs killed by one of the varieties of leptospirosis of North Queensland, in which a liver emulsion might show twenty to forty organisms to the dark-ground field.

After a guinea-pig recovered from the fever, leptospiræ usually appeared in the urine and persisted for a long time. At least fifteen out of seventeen of our guinea-pigs behaved in this way and became carriers. This is in accord with the behaviour of other leptospiral types. During the carrier stage most of the guinea-pigs appeared well, though a few failed to increase in weight. The day on which leptospiræ were first seen in the urine was noted in five animals. In these excretion began 13, 13, 14, 15 and 15 days after inoculation, which was six to eight days after the fever was over. The duration of the carrier stage has been studied in five animals. The original guinea-pig inoculated from J.H.G.'s blood still had leptospiræ in the urine 114 days after inoculation. In the others leptospiræ were found for the last time 94, 51, 41 and 35 days after inoculation.

The number of leptospiræ excreted varied from time to time. The numbers were fewer at the beginning and ending of the carrier period, when their excretion tended to be intermittent. At times the leptospiræ were present in enormous numbers, so that the urine resembled a culture. It is a curious fact that leptospiræ should be far more abundant in a guinea-pig after it has apparently recovered than when it is ill.

Other Laboratory Animals.

Two wild rats (*Rattus norvegicus*) were inoculated with infected guinea-pig liver. Both remained well in appearance and maintained their weight. The temperature of one remained normal, of the other was doubtfully raised. One was killed eight days, and one twenty days after inoculation. In neither were leptospiræ seen in the liver and kidney by dark-ground examination, although their presence in the rats was demonstrated by reinoculation of guinea-pigs. As far as these two experiments go, it appears that the rat may become a symptomless carrier with this as with other types of leptospira.

A rabbit (11) was inoculated with one mil of liver emulsion from an infected guinea-pig. It reacted after four days' incubation period with a fever of three days' duration. (Chart V.) Agglutinins for

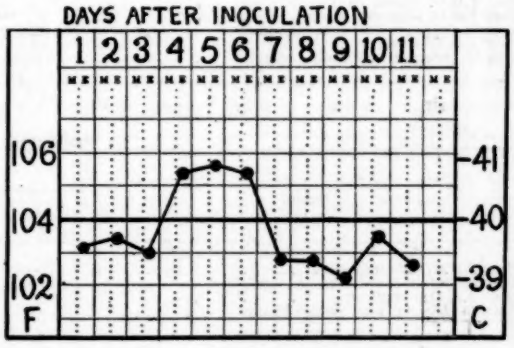

CHART V.
Temperature chart of rabbit 11. Seven-day fever.

the Pomona leptospira were found in its blood serum to a titre of 1,000 (+++) on the twenty-first day after inoculation, 300 (+++) on the twenty-ninth, and 30 (++) on the ninety-first. Leptospiræ were seen in the urine on the forty-eighth day, but not on the eighty-second. From rabbit 11 other rabbits were infected. Their behaviour was similar. Rabbit 10 had two days of fever after an incubation period of nine days. Its eyes became intensely congested. Rabbits killed during the fever did not show the characteristic lung hæmorrhages, nor could leptospiræ be seen in their organs. On the whole rabbits were much less susceptible to infection than guinea-pigs.

Four white mice were inoculated with a culture of the Pomona leptospira, but no sign of infection ensued. Temperature and weight remained normal. No leptospiræ could be seen in the livers and kidneys of two of them killed on the ninth and fourteenth

days, nor was the infection transmitted to guinea-pigs with these organs. No leptospiræ were found in the urine of the other two mice.

The Relation of the Pomona and North Queensland Leptospiræ.

The virulence for guinea-pigs of the Pomona strain of leptospira is low. Twenty of twenty-two animals survived inoculation. It is therefore much less virulent than some at least of the strains of leptospiræ of North Queensland. Cotter and Sawers[2] found that infection with the latter was regularly fatal in guinea-pigs. This we have confirmed. With a strain kindly sent to us by Dr. Cotter in 1935 we found that ten guinea-pigs died of eleven injected. And another North Queensland strain (Ballico), isolated by Dr. Cotter from a patient in Ingham and sent to us in 1936 by the courtesy of Dr. Lumley, of Townsville, killed every one of a series of five guinea-pigs injected, even though it had been sub-cultured for a year.

The striking difference in virulence between the Pomona and North Queensland leptospiræ suggests that they belong to different types. This conclusion is confirmed by cross-agglutination tests.

Table I shows results obtained by testing various sera with the Pomona strain, and Table II results with the Ballico strain. The results were read after three hours at 30° C. It will be seen that there is no cross-agglutination between the two strains. Our conclusions have received confirmation from Dr. Lumley, who writes: "Pomona strain does not belong to any groups we possess up here."

Although these two leptospiræ belong to different types, there is some degree of cross-immunity between them. A guinea-pig that has been infected with the Pomona strain of leptospira becomes immune to reinfection with the same strain. It also acquires a slight degree of protection against infection with the Ballico strain. In Table III it will be seen that five unprotected guinea-pigs inoculated with the Ballico strain all died. On the other hand, of five

Table I.

Agglutination with Pomona Strain.

Serum.	Titre.							
	10	30	100	300	1,000	3,000	10,000	30,000
Patient J.H.G. (fourth day)	−	−	−	−	−	−	−	−
Patient J.H.G. (eleventh week)	++	+++	+++	+	±	−	−	−
Rabbit 11 (injected with Pomona strain)	±	++	+++	+++	++	±	−	−
Patient J.J. (Innisfail)	±	−	−	−	−	−	−	−
Rabbit 15 (injected with Ballico strain)	−	−	−	−	−	−	−	−

Table II.

Agglutination with Ballico Strain.

Serum.	Titre.							
	10	30	100	300	1,000	3,000	10,000	30,000
Patient J.H.G. (eleventh week)	−	−	−	−	−	−		
Rabbit 11 (injected with Pomona strain)	−	−	−	−	−	−	−	−
Patient J.J. (Innisfail)	−	+++	++	+	±	−	−	−
Rabbit 15 (injected with Ballico strain)	+	+	+++	+++	+++	++	±	−

Table III.

Cross-Immunity Tests.

Dose of Ballico Strain Injected.	New Guinea-pigs.			Guinea-pigs Previously Infected with the Pomona Strain.		
	Number of Guinea-pig.	Weight in Grammes.	Result.	Number of Guinea-pig.	Weight in Grammes.	Result.
0·3 ml culture	1	253	Death, 5 days.	2	265	No apparent effect.
0·1 ml liver emulsion from guinea-pig 1 (6 leptospiræ per field)	3 5	275 307	Death, 5 days. Death, 5 days.	4	332	Death, 6 days.
0·1 ml liver emulsion from guinea-pig 3 (15 leptospiræ per field)	6	282	Death, 5 days.	7 8	303 315	Death, 10 days. Recovered after 5 days of fever.
0·1 ml liver emulsion from guinea-pig 6 (12 to 20 leptospiræ per field).	10	355	Death, 5 days.	11	320	Death, 8 days.
Average weight		294			307	

guinea-pigs that had previously undergone infection with the Pomona strain and were later injected with the Ballico strain, one showed no sign of infection, one recovered after five days of fever, and the other three died, surviving, however, rather longer than the unprotected guinea-pigs. The Pomona strain infection had therefore a slight protective influence against the Ballico strain.

This finding of a slight degree of cross-protection between leptospiræ of different types is in accordance with the classical work of Fletcher[3] in Malaya. He found that there was some affinity between all his different groups:

> If a guinea-pig recovers from an attack of leptospirosis, it becomes entirely immune to further inoculation of organisms belonging to the same group, and in addition it possesses a lesser degree of immunity against leptospiræ in other groups.

Some cross-immunity between different kinds of leptospiræ had also been observed by Inada[4] in Japan.

Relation of Pomona Strain to Foreign Strains of Leptospiræ.

A beginning has been made with the work of comparing this strain with those causing leptospirosis in other countries. This has been possible through the great kindness of Dr. Mertens, Director of the Geneeskundig Laboratorium, Batavia, in sending us cultures of a variety of types and their corresponding sera. Table IV shows the results of agglutination tests with the Pomona strain against the different sera. Tables V and VI show the results of agglutination tests with the Rachmat and Baermann leptospiræ. When they are compared with Tables I and IV, it will be seen that the Pomona organism is closely allied to these two, especially the former. But much more work remains to be done before its exact position in the genus *Leptospira* is established.

Summary and Conclusions.

A case of seven-day fever is described in a patient living near Pomona, South Queensland. The diagnosis of the case was based clinically on the similarity of the patient's symptoms to those of the seven-day fever of the East, and pathologically on the isolation of a leptospira from the patient's blood.

This leptospira proved to be different from a strain isolated in North Queensland. It was distinguished by its lower virulence and the absence of cross-agglutination. There exist therefore in Queensland at least two distinct kinds of leptospiral disease—the milder, seven-day fever, and the more severe kind with frequent jaundice and occasional deaths first described two years ago by Morrissey.[5]

Preliminary work suggests that the Pomona leptospira is related to the Rachmat and Baermann leptospiræ of Sumatra.

TABLE IV.
Agglutination with Pomona Strain.

Serum.	Titre.							
	10	30	100	300	1,000	3,000	10,000	30,000
Icterohæmorrhagiæ (classical Weil's), Wijnberg, Netherlands	−	−	−	−	−	−	−	
Canicola, Netherlands	−	−	−	−	−	−	−	−
Moscow	−	−	−	−	−	−		
Rachmat, Sumatra	+++	+++	+	±	−	−	−	−
Bindjei, Sumatra	−	−	−	−	−	−	−	
Baermann, Sumatra	+++	+++	++	±	±	−	−	
Batavia, Dutch East Indies	−	−	−	−	−	−	−	−
Andaman	−	−	−	−	−	−	−	−

TABLE V.
Agglutination with Rachmat Type, Palembang Strain.

Serum.	Titre.							
	10	30	100	300	1,000	3,000	10,000	30,000
J.H.G. (eleventh week)	+++	++	+	±	−	−		
Rabbit 11 (Pomona)	+	+++	+++	+++	+	±		
Rachmat	±	++	+++	+++	+++	++	++	±
Baermann	±	++	+++	+++	++	+	±	−

TABLE VI.
Agglutination with Baermann Type.

Serum.	Titre.							
	10	30	100	300	1,000	3,000	10,000	30,000
J.H.G. (eleventh week)	++	+	−	−	−	−		
Rabbit 11 (Pomona)	+	−	−	−	−	−		
Rachmat	+++	+++	+++	+++	+	±		
Baermann	+	++	+++	+++	+++	+++	++	−

This would appear to be the first proved case of seven-day fever in Australia, although the presence of this mild type of leptospirosis has previously been suspected.

While only one case has been proved by laboratory tests, there is clinical evidence that a number of cases have occurred from year to year in the same locality, which therefore represents an endemic centre of seven-day fever. This centre is about 700 miles further south than the endemic area of the more severe kind of leptospirosis.

One more definite entity has been differentiated out from the heterogeneous collection of fevers known as "coastal fever".

Acknowledgements.

We are indebted to Sir Raphael Cilento, Director-General of Health and Medical Services, Queensland, who long since predicted these findings, for permission to publish this work, and for contributing a foreword. We are grateful to Dr. W. K. Mertens, Director of the Geneeskundig Laboratorium, Batavia, for sending us a wide variety of cultures and their sera. We are indebted also to Dr. T. J. P. Cotter and Dr. G. F. Lumley, successive Medical Officers of the Commonwealth Health Laboratory, Townsville, for strains of northern leptospiræ, and to Dr. P. Mitchell, Chief Quarantine Officer (General), for his cooperation in this matter; also to Professor Harvey Sutton, of the School of Public Health and Tropical Medicine, Sydney, for assistance with the literature; and to Mr. A. S. Richards, Divisional Meteorologist, for the rainfall figure of Pomona. Finally, our thanks are due to Mr. H. E. Brown, who has undertaken the not inconsiderable duty of culturing and subculturing the various strains of leptospiræ.

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LEPTOSPIROSIS IN QUEENSLAND: A SEROLOGICAL INVESTIGATION LEADING TO THE DISCOVERY OF DISTINCT SEROLOGICAL GROUPS OF LEPTOSPIRÆ CAUSING LEPTOSPIROSIS AS IT OCCURS IN NORTHERN QUEENSLAND, WITH SOME OTHER RELATED OBSERVATIONS.

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The problems associated with the occurrence of leptospiral infections in man are very complex and numerous. These diseases are themselves almost cosmopolitan in distribution, and are not restricted to tropical regions. Diagnostic procedures in suitably equipped laboratories have been highly developed in the hands of trained personnel, and to the clinician himself spirochætal jaundice and allied infections are now much more readily recognizable; yet difficulties still remain, especially difficulties of diagnosis and epidemiology.

In June, 1936, the writer's interest was largely directed towards laboratory diagnostic procedures. In July of that year it was discovered that strains of leptospiræ existent in the Commonwealth Health Laboratory at Townsville, isolated from human patients and rats in Queensland, fell into two (possibly more) distinct serological groups. These groupings have, during the last six months, been explored fully within the limitations of available sera and cultures.

Some Notes upon the Serology of Leptospiræ.

Serological investigations upon the leptospiroses commenced with the discovery in 1914 by the Japanese workers, Inado and Ido, of *Spirochæta icterohæmorrhagiæ*. These investigations have been based upon protection experiments, Pfeiffer reactions, agglutination and adhesion tests *et cetera*. Rapidly it became evident that the so-called genus leptospira included a number of distinct serological groups and types which could be distinguished one from another by the above tests. Of considerable practical importance was the realization that at least some of these serological groups corresponded with definite and distinct clinical forms of the disease, for example classical Weil's disease, seven-day fever of Japan, and so on.

It is undoubted that, within a unit group of leptospiræ, type variations exist. The demonstration of types and their classification have not been productive of much result, because probably innumerable types exist, and in any case both animal and cultural passage tend towards alteration of type, and in some cases even of group, characteristics. Furthermore, the separation of types is very liable to yield different results, varying with the serological reaction and technique employed. Therefore, it has been customary for laboratory investigators to be more interested in establishing group classifications than in endeavouring to sort out innumerable types.

Group classification of leptospiræ is of importance for two reasons: firstly, their correlation with clinical forms of leptospiral infections, and secondly, the performance of diagnostic agglutination tests (for a serum may give a positive result with one group and a negative result with another).

In an investigation into the serological classification of leptospiræ, it appears usually that the investigator has been hampered by not possessing all the known world groups. Most examinations have been essentially in relationship to a local epidemic (perhaps in Europe or Japan or the Federated Malay States, for example), the presence of a local unit group or series of groups has been demonstrated and some correlation with other leptospiral strains has been made.

Perhaps the first truly practical (and also fairly complete) classification was that put forward by William Fletcher in 1928, based upon an investigation into leptospirosis occurring in the Federated Malay

States, and on the correlation of strains isolated in that area with other strains in his possession. Briefly, he demonstrated six distinct groups, of which the following four are listed:

(1) Group *icterohæmorrhagiæ*. Noguchi, Inada and Okell have isolated several strains which are included in this group.

(2) Group Akiyami *A*. This includes Inada's Akiyami *A* strain.

(3) Group Akiyami *B*. This includes Inada's Akiyami *B* strain.

(4) Group *pyrogenes*. This includes *Leptospira pyrogenes* Vervoort.

These four groups included typical Weil's disease (*Leptospira icterohæmorrhagiæ*), a form of Japanese autumn fever (*Leptospira autumnalis*, or Akiyami Type *A*), seven-day fever of Japan (*Leptospira hebdomadis*, or Akiyami Type *B*) and dengue-like fevers occurring in Sumatra (*Leptospira pyrogenes*, or *Leptospira febrilis*).

Taylor and Goyle published in 1931 an account of their work upon leptospirosis occurring in the Andaman Islands (Bay of Bengal), and showed that two distinct serological groups occurred in that area: Andaman's *A* group (which did not correspond to any of the four groups of Fletcher's mentioned above) and Andaman's *B* group (which corresponded to Fletcher's Akiyami *A* group). Consequently, to the abovenamed groups of Fletcher's the following can be added: (5) Group Andaman *A*.

There are several other leptospiral infections, for example swamp fever, occurring in Soviet Russia and Germany due to *Leptospira grippotyphosa* (allied antigenically with Akiyami Types *A* and *B* leptospiræ), and a leptospiral infection in dogs due to *Leptospira canicola* (allied antigenically to *Leptospira icterohæmorrhagiæ*).

Serological Technique Employed.

The technique employed in separating Queensland strains was essentially the microscopic agglutination test as elaborated by Professor Schüffner for use in leptospiral diagnostic procedures. It is to be understood, therefore, that the separation of Queensland strains has been effected by the agglutination phenomenon.

Since sera received for diagnostic testing are frequently (more often than not) infected, it has also been possible in almost all instances to observe collaterally with agglutination the adhesion test of Davis and Brown. Whilst no titre measurements according to the adhesion test are accurately possible in these collateral and accidental circumstances, nevertheless it is the writer's impression, based on his observations, that groups separated according to the agglutination response would almost certainly correspond to groupings as might be determined by the adhesion test.

Like all microscopic agglutination techniques, Schüffner's agglutination method (whilst qualitatively beyond criticism) is subject to the common disability of being quantitatively not so exact as a macroscopic method. For mass observations, the macroscopic method, however, is generally impracticable owing to the impossibility of providing over a period of time large volumes of leptospiral cultures. Further, what constitutes a standard for reading the end titre of agglutination will depend upon the individual standard of the observer (and in the one observer this will be found to vary unconsciously from time to time). Finally, the agglutinability of a unit type culture has been found to rise and fall sometimes according to the batch of media used (despite the media being prepared under standard conditions).

Bearing the above three factors in mind, absolute correspondence in the titres of agglutination of a specified serum, when put up against a number of strains of a unit group, is not to be expected.

Northern Queensland Leptospiroses.

Dr. A. H. Baldwin, in 1929, expressed the view that the ill-defined group of so-called "coastal fevers" occurring in Queensland might include a leptospirosis. Dr. G. C. Morrissey and Dr. T. Leckie suspected the presence of Weil's disease in the Ingham area in October, 1933. In August, 1934, Dr. T. J. Cotter and Dr. W. C. Sawers proved that an epidemic in that area was due to a leptospiral infection. Since 1934, several outbreaks of leptospirosis have occurred, not only in Ingham, but also in Innisfail and further north.

Sera and Cultures Investigated.

Sera that became available to the writer from time to time since June, 1936, came from patients contracting the disease in 1936, and also in some instances from patients who had been infected as far back as 1934.

Cultures existent in June, 1936, at the Commonwealth Health Laboratory had been isolated in 1934 and 1935, both from Queensland human patients and also rats. These cultures were added to late in 1936, both by the Townsville Laboratory and by Dr. R. Y. Mathew, of the Cairns Laboratory.

Overseas cultures were made available by the Director-General of Health, Dr. J. H. L. Cumpston, in 1936, through Dr. Paul Mitchell, who controls the Commonwealth Health Laboratories of the North-Eastern Division, and subsequently other cultures (overseas, one Queensland rat and one Queensland human) by Dr. E. H. Derrick, Director of the State Laboratory of Microbiology and Pathology, Brisbane.

Results of Agglutination Experiments.

Group A and Group B leptospiræ, isolated at this laboratory, have been tentatively named Group Australis *A* and Group Australis *B* (also corresponding sera).

Table IA demonstrates that sera from ten patients (P.1 to P.10) consistently produce agglutination with human strains C.1 to C.6, rat strains C.7 to C.12, and a pathogenic leptospira isolated from water, C.13. One apparent inconsistency is that of serum P.6, which records several negatives, but this serum was taken from a patient very early in the course of his illness when his agglutinins were very poorly developed.

Table IB demonstrates a complete inability for sera P.1 to P.10 to produce agglutinations with cultures of human strains C.14 to C.16, and rat strains C.17 to C.19.

TABLE IA.
Group A Human Sera+Group Australis A Cultures; Positive Agglutinations.

Human Serum.	Strains of Leptospiral Cultures.												
	C.1.	C.2.	C.3.	C.4.	C.5.	C.6.	C.7.	C.8.	C.9.	C.10.	C.11.	C.12.	C.13.
P.1	+	+	+	+	+	+	+	+	+	+	+	+	+
P.2	+	+	+	+	+	+	+	+	+	+	+	+	+
P.3	+	+	+	+	+	+	+	+	+	+	+	+	+
P.4	+	+	+	+	+	+	+	+	+	+	+	+	+
P.5	+	+	+	+	+	+	+	+	+	+	+	+	+
P.6	+	−	+	+	+	.	−	+	−	−	+	+	−
P.7	+	+	+	+	+	+	+	+	+	+	+	+	+
P.8	+	+	+	+	+	+	+	+	+	+	+	+	+
P.9	+	+	+	+	+	+	+	+	+	+	+	+	+
P.10	+	+	+	+	+	+	+	+	+	+	+	+	+

+ = positive agglutination; − = negative agglutination; . = no test carried out.

TABLE IB.
Group A Human Sera+Group Australis B Cultures: No Agglutination.

Human Serum.	Strains of Leptospiral Cultures.					
	C.14.	C.15.	C.16.	C.17.	C.18.	C.19.
P.1	−	−	−	−	−	−
P.2	−	−	−	−	−	−
P.3	−	−	−	−	−	−
P.4	−	−	−	−	−	−
P.5	−	−	−	−	−	−
P.6	−	−	−	−	−	−
P.7	−	−	−	−	−	−
P.8	−	−	−	−	−	−
P.9	−	−	−	−	−	−
P.10	−	−	−	−	−	−

Table IIA shows inability of sera from patients P.11 to P.24 to agglutinate cultures of strains C.1 to C.13; and Table IIB shows ability of sera from patients P.11 to P.24 to agglutinate cultures of strains C.14 to C.19.

Table III summarizes results set out in Tables IA, IB, IIA, IIB.

TABLE III.
Summary of Tables IA, IB, IIA and IIB.

Groups A and B Sera.	Groups.	
	Australis A. (C.1–C.13.)	Australis B. (C.14–C.19.)
Group A (P.1–P.10)	+	−
Group B (P.11–P.24)	−	+

From Table III two facts emerge: (i) Among 24 human sera examined, there were two contrasting agglutinin groups, Groups A and B. (ii) Among 19 strains of leptospiræ, there are two contrasting agglutinogenic groups, Groups A and B.

TABLE IIA.
Group B Human Sera+Group Australis A Cultures: No Agglutination.

Human Serum.	Strains of Leptospiral Cultures.												
	C.1.	C.2.	C.3.	C.4.	C.5.	C.6.	C.7.	C.8.	C.9.	C.10.	C.11.	C.12.	C.13.
P.11	−	−	−	−	−	−	−	−	−	−	−	−	−
P.12	−	−	−	−	−	.	−	−	−	−	−	−	−
P.13	−	−	−	−	−	−	−	−	−	−	−	−	−
P.14	−	−	−	−	−	.	−	−	−	−	−	−	−
P.15	−	−	−	−	−	−	−	−	−	−	−	−	−
P.16	−	−	−	−	−	−	−	−	−	−	−	−	−
P.17	−	−	−	−	−	−	−	−	−	−	−	−	−
P.18	−	−	−	−	−	−	−	−	−	−	−	−	−
P.19	.	−	−	−	−	−	−	−	−	−	−	−	−
P.20	−	.	−	.	−	.	−	.	.	.	.	−	.
P.21	−	−	−	−	−	.	−	−	−	−	−	.	−
P.22	−	−	−	−	−	−	−	−	−	−	−	−	−
P.23	−	.	.	−	.	.	−	−	.	−	−	.	.
P.24	−	−	−	−	−	−	−	−	−	−	−	−	−

TABLE IIB.
Group B Human Sera+Group Australis B Cultures: Positive Agglutinations.

Human Serum.	Strains of Leptospiral Cultures.					
	C.14.	C.15.	C.16.	C.17.	C.18.	C.19.
P.11	+	+	+	+	+	+
P.12	+	+	+	+	+	+
P.13	+	+	+	+	+	+
P.14	+	+	+	+	+	+
P.15	+	+	+	+	+	+
P.16	+	+	+	+	+	+
P.17	+	+	+	+	+	+
P.18	+	+	+	+	+	+
P.19	+	+	+	+	+	+
P.20	.	+	.	+	+	+
P.21	+	+	+	+	+	+
P.22	+	+	+	+	+	+
P.23	+	.	.	.	+	+
P.24	+	+	.	+	+	+

Of the sera submitted to this laboratory from patients in whom there was good presumptive clinical evidence of past or present leptospiral infection, an extraordinarily high percentage has yielded positive agglutinating power against either Group A or Group B leptospiral cultures. From this it may be deduced that the infecting leptospiræ in the Ingham-Innisfail region almost exclusively (if not entirely) belong to either Group A or Group B serological classification.

The Uniformity of Agglutinating Titres of Sera against Group A and Group B Cultures.

All the above sera tested have been tested to 1 in 30,000 dilutions. Variability of titre of agglutination of a particular serum against the member

strains of either Group A or Group B is a matter of interest, but not of great interest.

The defects of the microscopic agglutination technique have been already pointed out. To minimize variability in titre readings, the one observer alone has read the reactions. Rise and fall in the agglutinability of a particular strain have been frequently noted with the strains being examined, under circumstances quite apart from the strain becoming virulent or avirulent. In some measure (probably the greater measure) this variability is due to cultural environment, which can never be maintained at a constant standard. At the same time, the variability of titre is not gross, taking into account the limitations of the technique, which include errors of observation.

Tables IV and V show agglutination titres of a Group A and a Group B serum against the corresponding leptospiral groups. From these tables, all circumstances considered, a remarkable uniformity of titre is evident.

It thus becomes possible to formulate, in addition to the above two facts evident from Table III, a third statement: (iii) Of the strains within a single group (either Group A or Group B cultures) there is not only a group characteristic, but the strains themselves approximate antigenically very closely to each other (in fact some of the strains may be merely representatives of a single type).

Analysis of Group A Cultures.

Group A cultures comprise the following strains:

(A) Leptospiræ isolated from man:
- C.1. Isolated 1936, from Cairns Laboratory.
- C.2. Isolated 1934, Ingham.
- C.3. Isolated 1935, Ingham.
- C.4. Isolated 1935, Ingham.
- C.5. Isolated 1935, Ingham.
- C.6. Isolated 1936, from Cairns Laboratory.

(B) Leptospiræ isolated from canefield rats:
- C.7. Isolated 1934, Innisfail.
- C.8. Isolated 1934, Ingham.
- C.9. Isolated 1935, Ingham.
- C.10. Isolated 1935, Ingham.
- C.11. Isolated 1936, Ingham.

(C) Pathogenic leptospira isolated from water:
- C.13. Obtained by Dr. W. C. Sawers, School of Public Health and Tropical Medicine.

The last mentioned leptospira (C.13) was obtained by Dr. Sawers from a stagnant pool at the side of Halifax Road, near Ingham, in 1935, by immersing for forty minutes in this pool a guinea-pig, scarified on legs and abdomen. This guinea-pig died twelve days later with typical evidences of leptospirosis. This strain is not to be regarded as a water leptospira, but as a pathogenic leptospira deriving from rat contamination of this pool.

Analysis of Group B Cultures.

Group B cultures comprise the following:

(A) Leptospiræ isolated from man:
- C.14. Isolated 1935, Ingham.
- C.15. Isolated 1936, from Cairns Laboratory.
- C.16. Isolated 1935, Ingham.

(B) Leptospiræ isolated from canefield rats:
- C.17. Isolated 1935, Ingham.
- C.18. Isolated 1935, Ingham.
- C.19. Isolated 1935, Ingham.

The above analysis of cultures from Group A and Group B shows that within each group are both rat and human strains. It is more than a coincidence that all rat and human cultures from the Innisfail-Ingham area, and which are existent in this laboratory, should unfailingly fall into either Group A or Group B serological groups. It is generally believed that leptospirosis in man is caused by infection from rats. The existence of both Group A and Group B serological

TABLE IV.
Typical Agglutination Table of Group A Serum + Australis A Cultures.

Human Serum.	Leptospiral Culture.	Titres of Agglutination.							
		10	30	100	300	1,000	3,000	10,000	30,000
P.2	C.1	+	+	+	+	+	+	+	−
	C.2	+	+	+	+	+	+	−	−
	C.3	+	+	+	+	+	+	−	−
	C.4	+	+	+	+	+	+	−	−
	C.5	+	+	+	+	+	+	+	−
	C.6	.	.	.	.	.	.	.	.
	C.7	+	+	+	+	+	−	−	−
	C.8	+	+	+	+	+	+	−	−
	C.9	+	+	+	+	+	+	−	−
	C.10	+	+	+	+	+	−	−	−
	C.11	+	+	+	+	+	−	−	−
	C.12	+	+	+	+	+	−	−	−
	C.13	+	+	+	+	+	+	−	−
	(14–19) Group B	−	−	−	−	−	−	−	−

TABLE V.
Typical Agglutination Table of Group B Serum + Australis B Cultures.

Human Serum.	Leptospiral Culture.	Titres of Agglutination.							
		10	30	100	300	1,000	3,000	10,000	30,000
P.19	C.14	+	+	+	+	+	+	+	−
	C.15	+	+	+	+	+	+	−	−
	C.16	+	+	+	+	+	+	+	−
	C.17	+	+	+	+	+	+	+	−
	C.18	+	+	+	+	+	+	+	−
	C.19	+	+	+	+	+	+	−	−
	(C.1–13) Group A	−	−	−	−	−	−	−	−

strains in both man and rat is consistent with that view. And, furthermore, this is ground for thinking that a rat leptospira passaged through man probably will not change its agglutinogenic structure.

Relationship of Group A and Group B to other Queensland Leptospiræ.

In 1936 Dr. E. H. Derrick supplied to the writer two strains of leptospiræ, both isolated in 1936, one from a patient from Pomona, Queensland, the other from a Brisbane rat, called respectively strain Pomona and strain R.102. Dr. Derrick also made available an agglutinating rabbit serum prepared against Pomona strain.

Table VI shows that no agglutinations were recorded with either Group A or Group B sera. Table VII shows that Pomona rabbit antiserum is incapable of agglutinating Group A or Group B cultures. It is therefore deduced that a third distinct human leptospiral serological type exists in southern Queensland; also a fourth rat serological type (in Brisbane), as there are other evidences to suggest that Pomona and R.102 strains are themselves unrelated.

Relationship of Group A and Group B to Overseas Leptospira icterohæmorrhagiæ.

Two supposedly typical strains of *Leptospira icterohæmorrhagiæ* were available and tested. "Jackson", Number 4482, was obtained by the Commonwealth Health Department from the National Collection of Type Cultures, Lister Institute, London; *Leptospira icterohæmorrhagiæ* Wijnbergi and an antiserum prepared against it were supplied by Dr. Derrick, who obtained them from Dr. Mertens, Director, Geneeskundig Laboratorium, Batavia, Java.

Jackson, Number 4482, was originally isolated from a London patient suffering from Weil's disease. *Leptospira icterohæmorrhagiæ* Wijnbergi is a strain originally obtained from Professor Schüffner. It is non-virulent, and as such has been used as recently as 1936 by Dr. J. Smith and Dr. L. S. P. Davidson in determining the incidence of Weil's disease in fish workers in Aberdeen.

Table VIII shows the reactions of *Leptospira icterohæmorrhagiæ* Number 4482 and *Leptospira icterohæmorrhagiæ* Wijnbergi with Group A and Group B sera. No positive agglutinations could be obtained.

From Table IX it is apparent that an antiserum prepared against *Leptospira icterohæmorrhagiæ* Wijnbergi (titre 1 in 10,000) was incapable of agglutinating any member of Group A cultures; with Group B cultures this serum has in some instances the power to produce agglutination, but only in small titres (the highest, 1 in 100). On this evidence it may be said that Group A cultures have absolutely no relationship with *Leptospira icterohæmorrhagiæ* Wijnbergi, but that Group B cultures do show a distant relationship.

Relationship of Group A and Group B to other Leptospiræ from Overseas.

A number of other overseas cultures were available, and against them Group A and Group B sera were tested. With one exception no positive agglutinations could be obtained in this series. The important fact that became evident was that neither Group A nor Group B cultures (since Group A and Group B sera were negative) are related serologically to any overseas strains available.

Three of these strains, Akiyami *A*, Baerman, and CH.31 (Andaman's *B*) are group relations, and fall into Group IV of Taylor and Goyle, which corresponds to Group Akiyami *A* of Fletcher. Some-

TABLE VI.

Culture.	Group A Sera.						Group B Sera.							
	P.1.	P.4.	P.5.	P.8.	P.9.	P.10.	P.11.	P.12.	P.13.	P.15.	P.16.	P.20	P.22.	P.24.
Pomona	.	–	–	–	–	–	–	–	–	–	–	–	–	–
R.102	–	–	.	–	–	.	.	.	–	.	–	.	–	–

TABLE VII.

Serum.	Pomona Culture.	Group A Cultures.													Group B Cultures.					
		C.1	C.2	C.3	C.4	C.5	C.6	C.7	C.8	C.9	C.10	C.11.	C.12	C.13	C.14	C.15	C.16	C.17	C.18	C.19
Pomona rabbit agglutinating serum	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

TABLE VIII.

Culture.	Group A Sera.							Group B Sera.										
	P.1.	P.3.	P.4.	P.5.	P.8.	P.9.	P.10.	P.11.	P.12.	P.13.	P.14.	P.15.	P.16.	P.17.	P.19.	P.20.	P.22.	P.24.
4482, London	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Leptospira, Wijnbergi ..	–	.	–	.	–	–	–	.	.	–	.	.	–	.	.	.	–	–

TABLE IX.

Serum.	Group A Strains.													Group B Strains.						4482, London.	Leptospira Wijnbergi
	C.1	C.2	C.3	C.4	C.5	C.6	C.7	C.8	C.9	C.10	C.11	C12.	C.13	C.14	C.15	C.16	C.17	C.18	C.19		
Leptospira icterohæmorrhagiæ Wijnbergi antiserum	–	–	–	–	–	–	–	–	–	–	–	–	–	+ 1/50	–	–	+ 1/100	+ 1/50	+ 1/50	+ 1/10	+ 1/10000

what related to this group are the two Rachmat strains.

The dog type, Roesel (Holland) type, is presumably *Leptospira canicola* (Schüffner), the latter having a serological relationship to *Leptospira icterohæmorrhagiæ*.

Table XA shows the results of these tests.

Table XA shows completely negative results, including dog type Roesel (Holland) strain. The latter came from Dr. Mertens, Batavia, Java, and was kindly supplied by Dr. Derrick, Queensland State Health Department.

with the results obtained with dog type Roesel strain (which of course does not imply, for example, *vide* Schüffner's remarks above, that Roesel strain is not *Leptospira canicola*).

It is of interest to note Group B sera cross-agglutinating with *Leptospira canicola* (Wubbeling); that is, there is a suggestion that our Group B cultures are somewhat related to *Leptospira canicola*, which in turn is closely related to *Leptospira icterohæmorrhagiæ*. It is furthermore of interest to note the distant relationship of Group B strains to *Leptospira icterohæmorrhagiæ* Wijnbergi. (See Table IX.)

TABLE XA.

Cultures.	Group A Sera.					Group B Sera.			
	P.1.	P.4.	P.8.	P.9.	P.10.	P.13.	P.16.	P.22.	P.24.
To be regarded as one. Group IV (Taylor + Goyle), which is Group Akiyami *A* (Fletcher). Akiyami *A* strain (from Professor Miyagawa, Tokio)	–	–	–	–	–	–	–	–	–
Baermann strain (Sumatra)	–	–	–	–	–	–	–	–	–
Number 3542 strain (called CH.31—Taylor + Goyle)	–	–	–	–	–	–	–	–	–
Rachmat type, Bangkinang (Sumatra) strain	–	–	–	–	–	–	–	–	–
Rachmat type, Palembang strain	–	–	–	–	–	–	–	–	–
Batavia type, (Kandangan-Borneo) strain	–	–	–	–	–	–	–	–	–
Moscow strain	–	–	–	–	–	–	–	–	–
Dog type, Roesel (Holland) strain	–	–	–	–	–	–	–	–	–
English Rat, Number 3051, strain	–	–	–	–	–	–	–	–	–

Two types of leptospiræ occur in the dog; one is the ubiquitous *Leptospira icterohæmorrhagiæ*, and the other is *Leptospira canicola*. Both are capable of infecting man. *Leptospira canicola* is less pathogenic to dogs than *Leptospira icterohæmorrhagiæ*. There is a distinct serological relationship between these two leptospiræ.

Schüffner, November, 1931, in collaboration with Klarenbeck, isolated a dog leptospira from the urine of a Dobberman pincher. Schüffner has written ("Recent Work on Leptospirosis") as follows:

> The serological tests afford the most convincing evidence of the difference existing between the two strains (*canicola* and *icterohæmorrhagiæ*). The difference is very striking in cases in which the typical (*icterohæmorrhagiæ*) strain shows no cross agglutination with anti-dog strain serum or *vice versa*. In other instances there exists a certain amount of cross agglutination, which occasionally may become so marked as almost to obliterate the difference between the two strains, which are obviously closely related.

A strain, *Leptospira canicola* (Wubbeling), supplied through the courtesy of Dr. N. M. J. Jitta, President of the Superior Council of Health, Amsterdam, gives some cross agglutination (to a very small titre) against Group B sera, and is completely negative with Group A sera. This is somewhat at variance

Table XB tabulates the agglutination results of Group A and Group B sera with *Leptospira canicola* (Wubbeling) culture.

TABLE XB.

Anti-serum Group.	Patient.	Strain *Leptospira canicola* (W.). Titre of Agglutination.			
		10	30	100	300
Australis *A*	P.1	–	–	–	–
	P.10	–	–	–	–
Australis *B*	P.19	+	+	–	–
	P.22	+	+	–	–

At the time that the tests were carried out as in Table XB, P.1 had a titre against a group homologous strain of 1 in 300; P.10, 1 in 300; P.19, 1 in 1,000; P.22, 1 in 300.

Relationship of Group A and Group B to Ingham Water Leptospiræ.

In late 1936, Dr. D. W. Johnson, operating the Commonwealth Health Department's mobile unit, isolated from canefield irrigation drains and roadside

stagnant pools in the Ingham area nine strains of water leptospiræ. The method of isolation used was the well known coprozoic method of Hindle followed by Pasteur candle or Seitz filtration. It was hoped that some of these cultures isolated from water at Ingham would prove to be not the universal water leptospira, *Leptospira biflexa*, but possibly contaminating pathogenic leptospiræ from rats.

Table XI sets out the results of testing human positive sera from both Group A and Group B against these nine strains of leptospiræ from Ingham waters (canefield, or associated with canefield). It will be seen that none of the strains is capable of being agglutinated by Group A or Group B sera.

for he noted that two distinct pathogenic strains which had been maintained as stock cultures had reversed their serological types.

The position is that two conflicting views have been advanced: firstly that leptospiræ are relatively very stable; secondly that leptospiræ are very labile. Professor Schüffner emphasizes the serological specificity of strains of leptospiræ and the stability of their serological properties in culture.

At the Commonwealth Health Laboratory, strains of leptospiræ have been isolated in 1934, 1935 and 1936, and subsequently maintained in culture. All these strains, whether isolated in 1934 or 1936, definitely belong to either Group A or Group B.

Table XI.

Group.	Sera.	Water Leptospiral Strains.								
		C.20.	C.21.	C.22.	C.23.	C.24.	C.25.	C.26.	C.27.	C.28.
Australis *A*	P.3	–	–	–	–	–	–	–	–	–
	P.4	–	–	–	–	–	–	–	–	–
	P.5	–	–	–	–	–	–	–	–	–
Australis *B*	P.11	–	–	–	–	–	–	–	–	–
	P.17	–	–	–	–	–	–	–	–	–

The Stability of Serological Groups of Leptospiræ.

The stability of serological groups is a problem not alone confined to leptospiræ. An outstanding example of group alteration attendant upon prolonged laboratory cultivation was the conversion of *Proteus* Warsaw to *Proteus* Kingsbury.

The relative instability of certain genera would appear to depend not only upon laboratory cultural environment, but upon other factors such as virulence or attenuation of a strain, upon animal passage (including frequency of passage and the type animal selected).

It has been the practice at some laboratories to maintain leptospiral cultures, for use in agglutination tests, more or less virulent by passage through guinea-pigs every two months or thereabouts. One reason for so doing was the desire to maintain fixity of type and agglutinability. It would appear that this procedure has been successful in its object up to a point. Certain objections can be, however, raised.

It is well known that passaging a bacterial strain through a laboratory animal may result in a diminution or even total loss of agglutinability of that strain against its own antiserum. It is also well known that leptospiræ isolated from leptospirosis, not "Weil's" disease, may by frequent passage through guinea-pigs be elevated in pathogenic effects and virulence to the level of *Leptospira icterohæmorrhagiæ*. As an extreme example, Baermann and Zuelzer (1927) showed that, in their hands, a water leptospira isolated in Sumatra became virulent to guinea-pigs after repeated subpassage. Zuelzer noted that a water leptospira, previously agglutinating at a titre of 1 in 10,000 with a prepared antiserum, when passaged through a guinea-pig, became agglutinated to a titre 1 in 300, and still less when passaged a second time. On the other hand, Hermann, 1927, reported that serological changes might occur in laboratory strains of leptospira, It was a practice at Professor Schüffner's laboratory to passage his strains every few months through guinea-pigs, and it might be deduced that thereby serological stability was maintained. Generally speaking, it has not been the custom at the Townsville laboratory to passage cultures regularly through guinea-pigs; in fact some cultures have been kept solely in culture upwards of eighteen months without guinea-pig passage. There is no evidence as yet that any of the Townsville strains have changed their serological groupings (as evidenced by their agglutinogenic abilities). In fact, our strains have remained remarkably stable in type (though rise and fall in titre of agglutination within moderate limits have been observed). An important point is now stressed, namely that the great serological stability of these leptospiral strains in the writer's possession does not appear to depend upon frequent and regular passage of these strains through guinea-pigs (that is, does not depend upon maintenance of virulence).

The writer readily agrees that serological alteration of a specific leptospiral strain may occur; experience with his own cultures strongly supports the view that such changes must be of comparatively rare occurrence.

A possible criticism could be made on the lines of suggesting that all cultures represented in Group A and Group B were at the time of isolation merely members of one group, and that the separation of Group A and Group B is the accidental outcome of laboratory maintenance. Such is definitely not the case. Both years old cultures and cultures isolated but a few weeks from patients have definitely belonged to either Group A or Group B strains; above all, there is the proven circumstance that Group A and Group B sera exist in human patients (whether the sera were collected from long since recovered patients of 1934, or recently from convalescents).

Some Observations upon the Use of Therapeutic Antileptospiral Serum.

Considerable interest attaches to the use of antileptospiral serum in the therapeutics of leptospiral diseases. In Queensland, stocks of an antiserum prepared in England in 1934 have been available for several years.

Serum therapy in leptospiral infections has been warmly advocated by a number, and evidence has been gathered, both on clinical and laboratory grounds, to show that the use of serum may be effective in at least diminishing the severity of the illness. The effectiveness of an antiserum depends upon other qualities as well as its agglutinogenic powers. Yet it is common to estimate the value of an antiserum in terms of its agglutinating titre. One author considers that an antileptospiral serum, to be effective, should have a very high titre of agglutination. It was decided to determine what effect the antileptospiral therapeutic serum available in Queensland has upon Group A and Group B leptospiræ. Tables XII and XIII show the agglutinating effects of this antiserum upon Group A and Group B cultures.

TABLE XII.

Serum.	Group A Cultures.												
	C.1.	C.2.	C.3.	C.4.	C.5.	C.6.	C.7.	C.8.	C.9.	C.10.	C.11.	C.12.	C.13.
Antileptospiral serum (1934) ..	–	–	–	–	–	–	–	–	–	–	–	–	–

TABLE XIII.

Serum.	Group B Cultures.	Titres of Agglutination.				
		10	30	100	300	1,000
Antileptospiral serum (1934)	C.14	+	+	–	–	–
	C.15	+	–	–	–	–
	C.16	+	+	+	–	–
	C.17	+	+	–	–	–
	C.18	+	+	–	–	–
	C.19	+	+	+	+	–

It will be observed from Table XII that the therapeutic antiserum has no agglutinating power against any culture member of Group A strain. But with regard to Table XIII, it will be noticed that this serum possesses small titres of agglutination against Group B strain, varying from 1 in 10 with culture C.15 to 1 in 300 with culture C.19.

It becomes necessary here to interpolate a comment upon agglutination phenomena obtainable with leptospiræ when the microscopic technique is employed. The phenomena of agglutination as seen microscopically will be found to vary in some degree according to the characters (morphology especially) of the organism being agglutinated.

The author's experience of leptospiral agglutinations (based upon dark-ground examination of approximately 8,000 slides) leads to the conclusion that the appearances of an agglutination phenomenon may be said to be typical or atypical. The typical form may be complete or more usually incomplete (meaning that all or only a fraction of the leptospiræ are agglutinated); and, furthermore, the typical form is usually observable only with homologous leptospiræ and sera (using the term homologous in its wider sense). The atypical form (of which several subvarieties can be said to exist) is chiefly observable when the culture and the serum are heterologous (in other words, the atypical form is a cross-agglutination effect); it is also sometimes noted with homologous sera of exceedingly weak titre, and sometimes towards the end titre point of potent homologous sera.

With one exception, the results summarized in preceding tables were clear-cut positive or negative results (and when positive, always homologous). The exception is Table XIII. Here positive agglutinations are recorded; the important observation is that these small titre agglutinations, on the basis of their morphological appearances and manner of development, are almost entirely produced as the result of heterologous (cross) agglutination. This supposition is supported by the circumstance that the titres are very low.

To summarize, it is pointed out that this particular therapeutic antiserum available in Queensland, on the basis of agglutinating powers against local strains, may be regarded as quite useless when given to a patient suffering from a Group A infection, and may be of some small value when administered to a patient suffering from a Group B infection. In the latter case, if used, it should be employed in the maximum quantities (in the absence of other contraindications).

Should serum be considered necessary in treating patients of further outbreaks of leptospiral infection in northern Queensland, it is strongly represented that such a serum should be made from strains almost exclusively members of Group A and Group B.

Of course, Tables XII and XIII also further emphasize the serological separation of Group A and Group B (as also does Table XB), employing *Leptospira canicola* (Wubbeling).

Effect of Administering Antileptospiral Serum upon Subsequent Diagnostic Agglutination Tests.

It might be considered that the use of the antileptospiral serum under review might confuse subsequent diagnostic agglutination procedures, by reason of the patient's having bestowed upon his blood serum passive immune bodies. As this serum is of low titre (and also probably not homologous with local strains), and taking into consideration the considerable dilution that would occur after injection, it is not considered likely that any laboratory diagnostic confusion would arise; certainly no confusion could possibly occur in the case of a Group A infection. If it were the case, however, that administration of serum in large quantities could somewhat obscure the diagnostic side in a

Group B infection, then the confusion could be only temporary, as any passive immunity conferred lasts but a period of a few weeks. The following experiments were devised to illustrate the above point.

Serum of subject "L" was exhaustively examined and was found to have no agglutinins against either Group A or Group B cultures. Immediately after the withdrawal of serum for that testing, twenty cubic centimetres of the antileptospiral serum were administered to "L" subcutaneously in the thigh. Serum from "L" was withdrawn twenty-four hours later and reexamined for agglutinins; Table XIV summarizes the results. The "query positive" agglutinations were of very low titre and were most atypical. Serum from "L", eleven weeks later, showed no effects whatever against either groups of leptospirae.

TABLE XIV.

Serum.	Group A Cultures.	Group B Cultures.					
		C.14.	C.15.	C.16.	C.17.	C.18.	C.19.
Subject "L" withdrawn twenty-four hours after subcutaneous injection of 20 cubic centimetres of antileptospiral serum.	—	? + 1/10	—	? + 1/10	? + 1/10	? + 1/10	? + 1/20

Serum Sickness Following the Use of Antileptospiral Serum.

The administration of any serum, especially in large quantities, may be followed by ill effects of varying severity, and in this respect, of course, antileptospiral serum is not exempt.

Subject "L" had on other occasions received numerous injections of various vaccines, and on one occasion of anti-scarlatinal serum. No allergic reactions had been experienced by him, except in the case of typhoid, paratyphoid *A* and *B* vaccinations (when a moderate degree of post-vaccinal allergic response was experienced). There was no familial history of allergy.

This subject was given twenty cubic centimetres of antileptospiral serum subcutaneously. Four days later he experienced discomfort in the splenic region, motor restlessness, and swelling *plus* itchiness in the region of the injection (the thigh). On the fifth day weakness, muscle pains and an "explosive" more or less universal degree of urticaria developed, accompanied by considerable œdema of face and to a minor extent of the tongue. Within several hours of the cutaneous reactions appearing considerable dyspnœa was evident. Towards the close of the fifth day this subject's pulse became exceedingly rapid (almost uncountable) and thready, and sensation of impending unconsciousness was experienced. Injection of five minims of adrenaline solution produced dramatic improvement, but muscle pains rapidly recurred.

During the next thirty-six hours an exceedingly small quantity of urine was passed, to be followed for the succeeding two days by intense thirst and polyuria. (The urine had a specific gravity of 1002 to 1004.)

Muscle pains and restlessness continued in a severe form for upwards of three days after their inception, and it was interesting to note that these pains were considerably increased if a limb were placed in a dependent position. Aspirin produced no relief, and "Veramon" produced only a slight degree of relief.

This subject was confined to bed about five days, and on getting up found that he was unable to keep an arm or leg in a dependent and motionless position for more than about ten seconds without causing several muscular pains in the limb. Any circumstance producing congestion, for example a suspender or armlet, was productive of pain in the particular limb. This condition persisted about one week.

Albuminuria was transiently and intermittently present for about fourteen days after the illness manifested itself. Recovery was finally and rapidly complete.

There is nothing peculiar in the history related; the reaction may have occurred with any serum. It is felt, however, that if the subject "L" had also been severely ill from a leptospirosis, the added serum sickness might possibly have made the difference between a fatal issue or recovery.

Discussion.

From a solely serological standpoint no close relationship has been demonstrated to exist between Group A and Group B strains with any oversea or other Queensland leptospira. There is some evidence, however, to show that Group B strains are related distantly, in their antigenic structure, to *Leptospira icterohæmorrhagiæ* Wijnbergi. Table IX demonstrates this.

On the basis of testing local sera with *Leptospira icterohæmorrhagie* type strains Number 4482 (London) and Wijnbergi, no relationship of Group A or Group B sera to these type strains could be shown to exist. Here one must beware of arriving at a fallacious conclusion, for it is remotely possible that either Number 4482 or Wijnbergi, or both of them, are not truly representative, as they exist in culture in this laboratory, of true *Leptospira icterohæmorrhagiæ*. A remarkable fact is that Wijnbergi serum of a titre of 1 in 10,000 is capable of agglutinating Number 4482 to a titre of 1 in 10 only.

Professor Schüffner, Director of the Department of Tropical Hygiene, Royal Colonial Institute, Amsterdam, evidently regards (or regarded) *Leptospira icterohæmorrhagiæ* as a unit strain. In an address upon "Recent Work on Leptospirosis", he stated:

Up to 1931 we never encountered more than one strain of parasite, *Leptospira icterohæmorrhagiæ* (*icterogenes*). We compared it with the original strain from Berlin, London, Paris, Japan, the Dutch Indies, Lisbon, Hamburg, and found it typical in every respect. We likewise tested it with sera of patients we received from Greece, Copenhagen and the Belgian Congo, with the result that we were convinced that this strain occurs all over the world. It includes, moreover, the American strains of leptospirae we received from Noguchi and others under the name *Leptospira icteroides*, which Wenyon and Brown (1922) were the first to identify as *Leptospira icterohæmorrhagiæ*. The same typical strain we found in rats and dogs.

In the face of such a statement, it would be difficult to imagine that divergent original serological types of *Leptospira icterohæmorrhagiæ* exist. Yet the writer does entertain the idea that subspecies or varieties of *Leptospira icterohæmorrhagiæ* may in fact exist. Lieutenant-Colonel J. Taylor and A. N. Goyle, in their monumental work "Leptospirosis in the Andamans", in fact designated two subgroups, *Leptospira icterohæmorrhagiæ* Subgroup A and *Leptospira icterohæmorrhagiæ* Subgroup B, since Subgroup A serum could agglutinate Mulhuswamy Number 130 human strain, Kuala Lumpur, whereas Subgroup B serum could not.

Subgroup A included *Leptospira icterohæmorrhagiæ* Number 2545 (Lister Institute), whilst Subgroup B included *Leptospira icterohæmorrhagiæ* Number 142, Undain (Kuala Lumpur), which, it would appear, was included by Fletcher in his group *icterohæmorrhagiæ*. When it is remembered that Wijnbergi antiserum is almost impotent in agglutinating

Number 4482 strain (see Table IX), and whilst recognizing that the explanation may be merely that Wijnbergi or Number 4482 is no longer typical, yet the possibility of subtypes of *Leptospira icterohæmorrhagiæ* existing cannot be dismissed lightly.

It follows from the preceding paragraph that our Group B cultures may be a subtype of *Leptospira icterohæmorrhagiæ*. On this point, evidence is not sufficient to make a definite statement. For one thing, other "typical" *Leptospira icterohæmorrhagiæ* strains must be tested against Group B sera *et cetera*; and finally, there still remain other leptospiræ to be tested (for example leptospira Akiyami *B*, and more especially *Leptospira pyrogenes*).

The place of northern Queensland Group A and Group B strains is, at least on serological (agglutination) grounds, uncertain. No clear serological relationship to other leptospiræ has so far been worked out. The writer therefore has proposed, at least as a matter of convenience and subject to subsequent reclassification, that the name *Leptospira australis A* and *Leptospira australis B* be bestowed upon the Ingham-Innisfail Group A and Group B strains (from both man and rat).

Summary.

1. It has been shown that strains of leptospiræ isolated from man and rat in the Ingham-Innisfail area fall into two separate and distinct serological groups.

2. Similarly, all the sera of patients in the Ingham-Innisfail area so far tested fall into the two distinct agglutinating groups, which correspond exactly to the two groups of strains of leptospiræ.

3. Infecting leptospiræ in the Ingham-Innisfail region probably almost exclusively (if not entirely) belong to either Group A or Group B strain.

4. The strain members of a group are themselves almost identical one with another.

5. Each group contains both human and rat strains, and it would appear that passage of a rat strain through man does not materially alter its serological character as evidenced by agglutination phenomena.

6. Group A and Group B strains have been tentatively designated *Leptospira australis A* and *Leptospira australis B*.

7. *Australis A* and *B* are not related to Dr. E. H. Derrick's strains Pomona and R.102 (from southern Queensland).

8. *Australis A* and *B* are not related to nine water leptospiral strains isolated from Ingham water.

9. *Australis A* is not related to any oversea leptospiræ so far examined. But *Australis B* is distantly related to *Leptospira icterohæmorrhagiæ* (Wijnbergi, Netherlands) and to *Leptospira canicola* (Wubbeling).

10. Both A and B cultures, so far, have remained remarkably group-fast in successive subcultures over prolonged periods. Maintenance of virulence by frequent passaging through guinea-pigs does not appear essential to preserve agglutination characteristics.

11. *Leptospira icterohæmorrhagiæ* Wijnbergi does not behave serologically the same as *Leptospira icterohæmorrhagiæ* Number 4482 (Lister Institute) so far as these leptospiræ are concerned, as they exist in culture now at Townsville. This may be due to one or both changing their characteristics whilst being maintained in laboratories.

12. A therapeutic antileptospiral serum available in Queensland, from the viewpoint of its ability to agglutinate leptospiræ, would appear to be ineffective against *Leptospira australis A* infection, and not very effective against *Leptospira australis B* infection. The most active antiserum for use in Innisfail-Ingham patients would have to be made from *Leptospira australis A* and *B* antigen (or equivalent).

13. The therapeutic use of available antileptospiral antiserum does not affect the reading of agglutination tests made with serum withdrawn shortly after the administration of this antiserum.

14. Allergic reactions after the administration of antileptospiral serum may be experienced.

15. It is suggested, admittedly on not very strong grounds, that subtypes of *Leptospira icterohæmorrhagiæ* may exist, also perhaps subtypes of *Leptospira canicola*.

Practical Application of Findings.

In demonstrating the presence of two distinct serological groups of pathogenic leptospiræ in northern Queensland, and in finding so far no evidences of the existences of other strains in that area, the laboratory diagnosis of leptospirosis has been considerably simplified, and its value enhanced.

Except in very special circumstances, there are only two laboratory procedures of practical application in the diagnosis of leptospiral infection. It is obvious that from distant places blood from a patient is the only worthwhile specimen for sending to a laboratory. It is almost useless to endeavour to isolate leptospiræ from such a sample, even though it were taken under optimum conditions in the very few days during which leptospiræ occur in the blood stream. The two procedures practicable are agglutination and Pfeiffer reactions; of these two, the agglutination reaction must generally receive preference. Pfeiffer reactions require relatively large amounts of serum for their performance.

The importance of knowing that a patient suffering from leptospirosis in northern Queensland is infected almost certainly with either *Leptospira australis A* or *B* makes it simple to carry out an agglutination reaction with two cultures only (one *A* and one *B*). The result of such a test can be then interpreted with a good deal of confidence.

Finally, the determination of leptospiral groups in Australia is of practical importance in making it possible to prepare a more effective therapeutic antiserum for leptospirosis as it occurs here.

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THE DEFICIENCY ANÆMIAS.[1]

By JOHN A. MCLEAN, M.D. (Melbourne), M.R.C.P. (London),

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ON August 14, 1926, almost exactly ten years ago, Minot and Murphy announced in *The Journal of the American Medical Association* a successful treatment of pernicious anæmia, consisting in a diet including large amounts of liver. This discovery has brought forth a new conception of the anæmias. The recognition of the existence of certain factors essential to the normal formation of red blood corpuscles has led to a form of therapy in which these essential factors are supplied and what may be termed a deficiency anæmia is successfully treated. In a consideration of the disorders of the blood, it is to be remembered that the circulating blood and the bone marrow form one composite organ. Blood cells are being continually produced in the bone marrow and passed into circulation, and there is a very close relationship between the developing cells

[1] Read at a meeting of the South-Western Division of the Victorian Branch of the British Medical Association on August 8, 1936.

in the bone marrow and the mature cells in the circulation.

The red cells arise intravascularly in the intersinusoidal capillaries in the bone marrow. These capillaries are normally closed to the circulation, except at their openings, where the mature cells pass into the blood stream. Sabin has demonstrated the origin of red cells in the chick embryo from the lining endothelial capillaries. These very early nucleated red cells, which are found also in early human embryos less than one centimetre in length, were named by Ehrlich megaloblasts. Subsequently megaloblasts are replaced by erythroblasts, and in extrauterine bone marrow the formation of red cells is carried on by the multiplication of erythroblasts.

There is still much discussion among hæmatologists as to whether the megaloblast has a place in the normal development of the red cells in adult life. It is generally conceded that it is present in early embryonic life, and most observers follow Ehrlich in regarding the megaloblast as a pathological cell in extrauterine life.

Normally, the size of the red cell in the peripheral circulation is remarkably constant. It has been said that the size of a man's red cells remains in health as constant as his finger prints. In disease affecting erythropoiesis, imperfectly formed red cells are turned into the circulation, and the particular manner in which the red cell is abnormal indicates the manner in which normal erythropoiesis is disturbed. In anæmias due to iron deficiency the effect on the bone marrow is at the erythroblast stage of erythropoiesis. It is the function of the nucleus of the erythroblast to elaborate hæmoglobin in the cytoplasm of the cell, and when this function is complete the nucleus degenerates and is extruded. If this function is disturbed by lack of the necessary iron, cells with insufficient hæmoglobin are produced. These cells are less able to withstand trauma in the blood stream, and probably break up more readily into smaller cells or microcytes. The erythrocytes in stained preparations are pale, and show variation in size and shape with microcytosis. The blood picture is that of a hypochromic microcytic anæmia.

When the essential hæmopoietic principle or "P.A." factor is deficient, a different type of blood picture is produced. There is a reversion from the normal process in which erythropoiesis is maintained by a proliferation of erythroblasts, to the embryonic mode of cell production in which megaloblasts predominate as the precursors of the erythrocytes. The mature red cells are larger than normal, and, as there is no deficiency of iron, the cells have a normal concentration of hæmoglobin. These large cells are not well adapted to the stresses in the rapidly moving blood stream, and it is probable that they break up into smaller cells and fragments. In stained films the red corpuscles take the stain well and show anisocytosis with megalocytes. The blood picture is that of a hyperchromic megalocytic anæmia.

The Size of Erythrocytes.

Estimation of the size of red blood cells is, therefore, of considerable importance in the diagnosis of the deficiency anæmias. The most accurate method is by direct measurement of red cells in a stained film and by plotting the results as a graph. This is the Price-Jones curve, but it is a time-consuming method, and is not suitable as a routine clinical procedure.

The diffraction method, in which the Eve halometer is used, is useful and convenient in diagnosing megalocytic anæmia and familial acholuric jaundice, but it cannot be relied on absolutely. Occasionally I have had cases in which the halometer reading was normal, but which in other respects were typical of pernicious anæmia and showed the usual response to liver therapy. It is said that the diffraction method determines the diameter around which the greatest number of cells is distributed. This is not necessarily identical with the mean diameter, and in rare cases of pernicious anæmia, in which anisocytosis is more marked than macrocytosis, the halometer may give a normal reading.

Another method for determining the size of the red cells is by the hæmatocrit. The hæmatocrit enables one to measure the relative corpuscular volume by centrifuging at a given speed for a definite length of time a column of oxalated blood contained in a glass tube. The corpuscular volume is read from the tube, and from this reading other values are calculated. Thus, if the volume occupied by the packed red cells of a given volume of blood is known, and also the number of cells in that volume of blood is calculated from the red cell count, the mean volume of the individual red cells is obtained by dividing the corpuscular volume by the number of cells. This value is known as the mean corpuscular volume. Similarly, when the hæmoglobin value of a given volume of blood and the corpuscular volume of the same quantity of blood are known, by dividing the former by the latter and expressing the result as a percentage the concentration of hæmoglobin in the individual red cells is obtained. This is the mean corpuscular hæmoglobin concentration.

Another value which has been found to be useful is obtained by dividing the hæmoglobin value of a certain volume of blood by the number of cells in the same volume. This gives the mean corpuscular hæmoglobin. This value gives the same information as the colour index. The manner in which these three determinations are actually obtained from the hæmatocrit reading and the red cell count is shown in the accompanying table.

Classification and Causation of Anæmias.

On the basis of hæmatocrit determinations, Wintrobe classifies anæmias into four groups: (*a*) macrocytic, (*b*) normocytic, (*c*) microcytic, (*d*) hypochromic microcytic. This classification is based on the morphology of the red cells. It would be more logical to classify anæmias according to their ætiology.

Anæmia may be due to three main causes: (i) faulty production, (ii) excessive destruction in the peripheral circulation, (iii) loss of blood by hæmorrhage.

Anæmias due to faulty production have been termed dyshæmopoietic anæmias by Vaughan, who states that such anæmias may be due to a deficiency

Determination.	Method of Obtaining Determination.	Method of Expression.
Mean corpuscular volume..	$\frac{\text{Volume of packed red cells per thousand cubic centimetres of blood}}{\text{Red cells in millions per cubic millimetre.}}$	As cubic microns.
Mean corpuscular hæmoglobin	$\frac{\text{Hæmoglobin in grammes per thousand cubic centimetres of blood}}{\text{Red cells in millions per cubic millimetre.}}$	As micro-microgrammes.
Mean corpuscular hæmoglobin concentration.	$\frac{\text{Hæmoglobin in grammes per hundred cubic centimetres of blood}}{\text{Volume of packed cells in cubic centimetres per hundred cubic centimetres of blood}} \times 100$	As percentage.

of factors necessary for erythropoiesis, to the presence of factors disturbing erythropoiesis, or to exhaustion of bone marrow by over-stimulation. The known factors necessary for erythropoiesis are iron and traces of copper, the "P.A." factor, vitamin *C*, thyroxin.

Anæmia due to Iron Deficiency.

The developing fœtus obtains iron from the mother and the mineral is stored in the liver. Bunge has shown that weight for weight there is five times as much iron in the liver of new-born as in the liver of adult animals. This store of iron is necessary to tide the infant over the period when the diet is deficient in iron. The margin of safety in iron derived from milk is extremely small, so that anything but a regular full feed of breast milk from a mother receiving an adequate diet will tend to produce nutritional anæmia. As a prophylactic measure, Dr. Helen Mackay recommends the addition of four to nine grains of iron and ammonium citrate every day. Others attack this problem of nutritional anæmia in infancy by weaning the child at an earlier age. Broths and vegetable *purées* are added to the diet at three months; at six months, egg yolk and fish are added, and a little later, red meat. Dr. Mackay not only demonstrated the efficacy of iron in the prevention and treatment of nutritional anæmia in infancy, but she showed that the morbidity rate in children treated with iron was half that of untreated controls. Colds, otorrhœa, bronchitis and enteritis were twice as common in untreated babies, and such infections aggravate the anæmia, which may develop rapidly and terminate fatally.

Idiopathic hypochromic anæmia and hypochromic anæmia of pregnancy are the other important iron deficiency anæmias. It is largely owing to the work of Witts that this group of anæmias has been recognized and successfully treated. Chlorosis is also an iron deficiency anæmia, but it is practically non-existent today. At puberty, unless the diet is specially rich in iron, there is apt to be a transient anæmia which passes off as the rate of growth slows down and bodily function becomes stabilized in the adult condition.

Idiopathic hypochromic anæmia is found chiefly in middle-aged women, and is characterized by a low colour index; achlorhydria and glossitis are usual, whilst koilonychia is common and splenomegaly is not uncommon. Davidson has shown that this type of anæmia with hæmoglobin below 70% is present in approximately 14% of women of the poorer classes in Aberdeen. The complete syndrome of idiopathic hypochromic anæmia is rare in Australia, no doubt owing to the better living conditions and a higher standard of diet. Achlorhydria is found in 80% of cases, and Witts stresses this factor in the ætiology of the condition as causing defective digestion and assimilation of iron. Apperly has shown that there is a direct relationship between the number of red cells in the blood and the gastric acidity. When the red cells fall to one-half or two-thirds normal, free acid disappears from the stomach, and Apperly states that one must distinguish between the achlorhydric anæmia of Witts and anæmic achlorhydria.

Hypochromic anæmia may occur in pregnancy, and it is important to diagnose and treat the condition, for if untreated, the mother is more liable to puerperal infection and the baby will have an insufficient store of iron and will more readily develop nutritional anæmia during infancy.

The treatment of these hypochromic anæmias consists of the administration of iron in large doses. It has been shown in animal experiment that traces of copper are also necessary. It appears that all compounds of iron must be broken down into simple salts before the iron can be assimilated. Iron is absorbed chiefly in the duodenum, but the stomach and the whole of the small intestine may take part in the process. The available iron of the food is probably reduced to the bivalent ferrous state in the alimentary tract. After absorption, iron is apparently stored in the liver and is taken up by the nuclei of the erythroblasts, which elaborate hæmoglobin. An interesting fact in the therapy of iron is what has been termed the threshold phenomenon. A patient may be treated for many weeks with a daily dose of 30 grains of iron and ammonium citrate with no apparent effect, but on raising the dose to 60 grains a day a reticulocyte crisis occurs and the anæmia is steadily repaired. The therapeutic activity of preparations of iron is proportional to their solubility and the ease with which ferrous ions are produced. It is probable that ferric salts are reduced to ferrous salts in the alimentary tract before absorption. Unfortunately the soluble ferrous salts are irritating to the stomach and tend to become oxidized in solution. The ideal iron preparation is yet to be found. As a routine, I give the scale preparation *Ferri et Ammonii Citras* in doses of 30 grains three times a day after food, or *Pilula Ferri Carbonatis* (five grains in each pill) in 15 grain doses three times a day.

Excess of iron has no effect in normal persons in provoking blood formation, and as pointed out by

Witts, iron acts as a nutrient, not a stimulant, to the bone marrow.

Anæmia due to a Deficiency of the "P.A." Factor.

Hyperchromic megalocytic anæmia occurs when there is a deficiency of the "P.A." factor. This "P.A." factor is produced in the stomach by the interaction of an intrinsic factor in the gastric juice and an extrinsic factor present in certain foods, such as beef, egg yolk, wheat germ and autolysed yeast. The exact chemical nature of these two factors is unknown. The work of Meulengracht indicates that the intrinsic factor is produced at the pyloric end of the stomach and the first part of the duodenum, and there is reason to believe that this factor is secreted by the pyloric glands in the stomach and the Brunner's glands in the duodenum. The "P.A." factor is absorbed from the intestine and is stored in the liver.

Hyperchromic megalocytic anæmia may be due to four causes:

1. Deficiency in the gastric and duodenal secretion of the intrinsic factor. This is the most common cause of this type of anæmia and is seen in Addison's (pernicious) anæmia, in which *achylia gastrica* is present.
2. Deficiency of extrinsic factor in the food. This occurs in tropical pernicious anæmia, and has been found amongst the native population in India, where the diet is inadequate. This anæmia is cured by "Marmite", an autolysed yeast product particularly rich in the extrinsic factor.
3. Faulty absorption of the "P.A." factor from the alimentary tract. This occurs in cases of fatty diarrhœa, sprue and cœliac disease.
4. Failure of the liver to store the "P.A." factor. This occurs in certain cases of cirrhosis of the liver in which gross liver damage is present.

The clinical syndrome in hyperchromic anæmia may be most diverse. At one time pernicious anæmia was regarded as a distinct disease entity with a circumscribed syndrome and a typical blood picture. Today it is recognized that anæmia due to a deficiency of the "P.A." factor does not always present the same clinical syndrome and the diagnosis can be made only on the blood picture.

Hyperchromic anæmia occasionally occurs in association with pregnancy, but is much less common than hypochromic anæmia. It is believed to be due to a temporary lack in the gastric juice of the intrinsic factor, but in certain instances lack of extrinsic factor in the diet may be the important ætiological mechanism.

The treatment of hyperchromic megalocytic anæmia is the administration of the "P.A." factor. It is important that in the ordinary case of pernicious anæmia (Addison's anæmia) the treatment be continued and the patient kept under constant observation for the rest of his life. The disease should be regarded in the same way as *diabetes mellitus*. I have seen several cases in which the disease was recognized, the patient was told to take half a pound of liver a day, and then left to his own resources. The inevitable happened; liver was given up and the final condition of the patient, crippled with subacute combined degeneration of the cord, was worse than the first. Another important point is that different preparations vary in potency. I have recently seen two cases in which no response was obtained from intramuscular injections of two locally manufactured preparations, and in each case a satisfactory response was subsequently obtained from "Campolon" injections. In the ordinary case I usually give an intramuscular injection of ten cubic centimetres of "Campolon" and repeat the dose in three weeks; thereafter an injection is given every month. There are two disadvantages in this method of treatment: (i) There is often cramp-like pain at the site of injection and radiating down the leg, which takes some hours to wear off. (ii) Occasionally an anaphylactic reaction occurs. It is probable that when the "P.A." factor is isolated in pure form, these inconvenient reactions will be avoided. A new preparation, "Anahæmin", is claimed to be about five times as potent as "Campolon".

Occasionally one comes across a case of hyperchromic anæmia which does not respond to treatment. Wilkinson has named these "acresthic anæmias", on the assumption that there is an inability to utilize the "P.A." factor.

Anæmia due to Deficiency of Vitamin C.

A hypochromic anæmia is usually present in scurvy and this anæmia is unaffected by treatment with iron or liver, but is cured by adequate amounts of vitamin *C*.

Anæmia due to Deficiency of Thyroxin.

Anæmia is usually present in myxœdema, and the type of anæmia may be hypochromic or hyperchromic. Thyreoid extract induces a reticulocyte response and the anæmia is repaired. Sometimes in pernicious anæmia there is an associated thyreoid deficiency and the anæmia is not completely repaired until thyreoid extract is given as well as liver. This possibility should be considered in cases of pernicious anæmia which do not respond satisfactorily to liver.

Conclusion.

In conclusion, I wish to stress the importance of the alimentary tract in the ætiology of anæmia. The iron in the food is probably converted into the soluble ferrous chloride by the action of hydrochloric acid secreted by the glands in the fundus of the stomach. This ferrous chloride is then absorbed chiefly in the duodenum, but also in the stomach and intestine. The pyloric glands and Brunner's glands in the duodenum secrete the intrinsic factor, which interacts with the extrinsic factor in the food and produces the "P.A." factor. The "P.A." factor is absorbed in the duodenum and intestine and is stored in the liver. In operations on the stomach and duodenum, the importance of this region of the alimentary tract in erythropoiesis should be remembered. Most intractable anæmia may occur in patients in whom the gastric juice has been reduced and the hæmopoietic area of the stomach and duodenum has been side-tracked by gastro-enterostomy. The anæmia is usually hypochromic;

its onset is insidious and it may not be manifest until some years after the operation. It is more common in women and is not directly related to the extent of the operation. The reason why anæmia occurs in some cases and not in others is not known. Presumably it is due to an upset in normal physiology of digestion. The secretion of gastric juice may be deficient, but is not always deficient, and it is more probable that the anæmia is due to faulty absorption from the duodenum and intestine. There is another factor in that the diet of these patients is frequently deficient in iron-containing foods.

Reviews.

A CLINICAL HANDBOOK.

Too little use is generally made of standardization of technique in medical investigation and treatment, especially in large institutions. It is therefore pleasing to see the "Clinical Handbook for Residents, Nurses and Students" of Saint Vincent's Hospital, Sydney, reach a second and revised edition.[1] The book contains a wealth of good subject matter which is generally well set out and devoid of padding.

It might be regarded as somewhat risky to combine instructions for nurses and resident medical officers in one volume. Our experience, however, is that the average resident medical officer is appallingly ignorant of nursing technique; and for this reason, when he ventures into private practice, many a young practitioner will be very glad to have this volume with him. On the other hand, we feel that the nurse has been in some ways neglected at the expense of the resident medical officer and student. This is seen in the section on anæsthesia, where, as is usually the case, the very important rôle of the nurse is almost completely ignored. One cannot, for instance, overemphasize the importance of a nurse knowing just what not to do during an induction. In our experience, given a reasonably skilled anæsthetist, the nurse who does not understand her job is a common cause of stormy inductions.

A book of this nature must necessarily be only supplementary to the larger standard text-books, and we feel that certain sections might well have been eliminated. It is very difficult to see any good purpose being served by the chapter "Index for Laboratory Examinations", unless it is to shield the "spot" diagnostician.

Much of the section on anæsthesia would have been better eliminated. The latter part especially of this section is so incomplete as to be misleading and even dangerous. Every anæsthetic should be regarded as a serious matter, and inadequate descriptions, such as those given, allow resident medical officers to underestimate the risks, particularly of special techniques and anæsthetic drugs. This subject can be covered only by books devoted wholly to anæsthesia.

The widely differing styles of the various contributors have not been edited sufficiently evenly to make good study reading, but the book is intended for reference and should find a place in the staff-room of every ward. Some excellent tables are given, the print and make-up are good, and, despite the criticisms given, the book can be thoroughly recommended.

[1] "Clinical Handbook for Residents, Nurses and Students, Being the Routine Methods of St. Vincent's Hospital, Sydney", by Members of the Staff of the Hospital; edited by V. M. Coppleson, Ch.M., F.R.C.S., F.R.A.C.S., and D. Miller, Ch.M., F.R.C.S., F.R.A.C.S.; Second Edition; 1936. Australia: Angus and Robertson Limited. Crown 8vo, pp. 215. Price: 6s. net.

SOCIAL HYGIENE.

"SOCIAL HYGIENE TO-DAY", by Henry Ernest Garle, is a book consisting of two parts.[1] It ought to appeal to that section of the medical profession which is interested in public health. Mr. Garle is not a member of the medical profession, but a barrister of the Middle Temple, and he writes with authority upon the whole position of prostitution and venereal disease in their social and economic aspects.

Part I consists of ten chapters dealing with the social aspect of prostitution and venereal disease. Mr. Garle advances the thesis that social hygiene, in its fullest application, is an art—an art dependent, of course, upon scientific knowledge and the interpretation of certain social facts. Chapter II is concerned with prostitution, and the author briefly traces its growth and the various theories put forward to explain the custom. This chapter is less convincing than the remainder of the book, for there is no mention of the psychology of prostitution or of prostitutes. This is a very serious omission, for there can be no full understanding of a human institution or of a human being without some insight at least into the mental factors associated with or responsible for the institution or the living being who has developed the institution.

The chapters on international developments are interesting, and valuable contributions to the history of the legal aspects of control of prostitution and venereal disease. The author presents a strong case against control by regulation—the registration and medical examination of prostitutes.

Chapter X deals adequately with the present position of prostitution and venereal disease, and gives the statistical results of inquiries in Great Britain and France into the prevalence of disease. In 1928 the Vernes Institute of Paris alone reported 13,171 new cases of syphilis, whereas in Greater London 5,270 new cases were reported. It would appear that the incidence of new syphilitic infections is about six times greater in Paris than in London.

Part II of the book is a very remarkable digest of the laws of all, or practically all, civilized nations on venereal disease, and in such nations as America and Australia even the State laws are epitomized. The amount of work done by the author in this part is tremendous, and reflects great credit on his learning and on his capacity for hard work.

The final part of the book consists of eleven appendices dealing with international agreements regarding facilities to be given to merchant seamen, specimen syllabus for lectures to parents, educationists *et cetera*.

The whole book is concluded by the addition of a very comprehensive bibliography and index. The author is to be congratulated upon a fine work; it should receive a wide circulation amongst public health officials.

Notes on Books, Current Journals and New Appliances.

A GUIDE TO THE ADDENDUM TO THE BRITISH PHARMACOPŒIA.

WHEN the British Pharmacopœia was published in 1932, British Drug Houses Limited issued a guide to that volume. The guide was so much appreciated that the same firm has issued a guide to the recently published "Addendum" to the British Pharmacopœia. The second guide is a pamphlet of eleven pages and will be most useful to medical practitioners. A copy will be forwarded gratuitously to any medical practitioner who cares to apply to British Drug Houses (Australia) Limited, at 250, Pitt Street, Sydney.

[1] "Social Hygiene To-Day", by H. E. Garle; 1936. London: George Allen and Unwin Limited. Demy 8vo, pp. 387. Price: 12s. 6d. net.

The Medical Journal of Australia

SATURDAY, MAY 1, 1937.

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HORMONAL TREATMENT IN OBSTETRICS AND GYNÆCOLOGY.

SIR STANTON HICKS, in his article on the interrelationships of the sex hormones, contributed last December to this journal at our request, stated that, provided the hormones were used with appropriate physiological care and knowledge, they would produce the results for which they were given. This is not realized by all practitioners of medicine. Many may, as Sir Stanton Hicks suggested, be bewildered at the mention of the word hormone; others doubtless have not bothered to study the question of hormone therapy, either because they are so conservative that they wait until everyone else is using a method before they adopt it, or because they are foolish enough to distrust a method of therapy that is constantly being pushed before them by travelling agents of drug houses. Those who have followed the literature on the subject and who have applied their knowledge with care and discernment, know that good results can be obtained. It was to stimulate interest in the clinical use of hormones that Sir Stanton Hicks was asked to write for this journal. There is need for the awakening of interest, for, as E. C. Dodds stated at a recent discussion of the Section of Obstetrics and Gynæcology of the Royal Society of Medicine,[1] if obstetricians and gynæcologists will not try to use hormonal products, others will undoubtedly take advantage of the opportunities provided by their use. Dodds was insistent that the substances provided for clinicians by biologists and chemists could not be ignored. He said that if clinicians did not get satisfactory results with these substances, it was their own fault. There was some excuse for not knowing how to use them, since their introduction was relatively recent, but there was no excuse for not trying.

The discussion at the Royal Society of Medicine was "on the present position of hormones in obstetrics and gynæcology"; it will serve as a useful introduction to the subject for those who have not given it much consideration. The several speakers gave a good idea of the possible results of treatment, and the views expressed were sufficiently divergent to show that in many respects finality has not been reached and that care in the selection of patients and in the application of the remedy is necessary. P. M. F. Bishop laid emphasis on two important principles. The first was that in any case of endocrine deficiency it was necessary to consider not only defective secretion of the endocrine gland, but also defective utilization of the secretion by the appropriate tissues. The second was the need, in the evaluation of the results of endocrine therapy, for sharp differentiation between local treatment and systemic treatment. As H. Gardiner-Hill insisted, endocrine therapy is essentially substitution therapy, for endocrine extracts do not stimulate the glands that secrete them. Most hormonal treatment is therefore what Bishop calls local treatment; in other words, its effect lasts only during the period of administration of the hormone. Systemic treatment, if successful, will lead to readjustment of the disordered balance of the endocrine system as a whole.

[1] *Proceedings of the Royal Society of Medicine*, January, 1937.

Gardiner-Hill named some of the available sex hormones and said that they were all of definite potency; he did not say that his list was a complete one. He divided œstrin preparations into three main types, namely, keto-hydroxy-œstrin, di-hydroxy-œstrin and tri-hydroxy-œstrin. In the first group are the commercial preparations "Menformon", "Œstroform", "Theelin", "Progynon" and "Unden"; in the second group are "Dimenformon", "Œstroform B" and "Progynon B"; "Theeol" is a preparation of the third group. Preparations of the *corpus luteum* include "Progestin", "Proluton" and "Lutren". "Antuitrin S", "Prolan" and "Pregnyl" are gonadotropic substances. Sex hormones may be used with advantage in certain forms of secondary amenorrhœa. They are often effective also in the treatment of functional uterine hæmorrhage (*metropathia hæmorrhagica*). T. N. A. Jeffcoate maintained, and enthusiasts would do well to take note of his contention, that in only 66% of cases was functional uterine hæmorrhage adequately controlled by hormonal therapy. He has found that 33% of patients so affected have a recurrence of symptoms within a comparatively short period of time. The treatment is, he holds, most useful in puberty hæmorrhage, success being obtained in 80% of cases; it is least effective in patients over the age of forty. Hormonal treatment is of little use in menopausal hæmorrhage. Œstrin therapy is particularly useful in the induction of abortion or labour when the fœtus dies *in utero*; it is most successful if the pregnancy is far advanced and the fœtus has been dead for a relatively short period of time. In threatened abortion the use of the appropriate hormone may check the uterine contractions that are tending to expel the fœtus; prophylactic therapy also, by preventing undue uterine motility, may in the early months of pregnancy be effective in habitual abortion. In dysmenorrhœa hormonal therapy is occasionally effective, but, on account of the large psychological element that is always present, great care must be exercised in attributing the result to the hormone. In the menopausal syndrome even small quantities of œstrin given by mouth are sometimes found to be sufficient to control hot flushes, headaches and dizziness; larger doses have a miraculous effect on such sequelæ as *pruritus vulvæ*, atrophic senile vaginitis and vaginal ulceration and kraurosis. Finally, obstetricians should remember that œstrin is often useful in uterine inertia; Jeffcoate has found that 50% of patients suffering from inertia receive benefit from injections of œstrin.

The subject of hormone therapy cannot be left without some reference to the possible dangers of giving large doses. Dodds draws attention to the view that the chemical structure of hormones bears a certain resemblance to that of the carcinogenic hydrocarbons and that there may be a danger in this direction. He points out that œstrone and its derivatives have no carcinogenic activity when tested in the same way as the carcinogenic hydrocarbons; they must therefore be acquitted in terms of definition of carcinogenicity. On the other hand, there is evidence that if infantile mice are injected from birth to adult life with large quantities of œstrone, the incidence of carcinoma of the mamma increases. In reply to this observation, Dodds states that this increase occurs only in susceptible animals. Similarly, the production of sarcomata by the subcutaneous injection of œstrone has been described. In this regard Dodds states that these experiments bear no relationship to the physiological employment of hormones; he thinks that it is unjust to limit the action of hormones on this account. There is no gainsaying his argument when he points to the excellent results obtained in the hormonal treatment of kraurosis of the vulva, a condition commonly regarded as pre-cancerous. Hormonal therapy is yet in its infancy, and with time more effective products will be forthcoming. In the meantime no medical practitioner should neglect the proven weapons that are at his disposal.

Current Comment.

SHOCK.

MANY of the familiar concepts and entities in medicine are not easy to define; this may be due to inherent difficulties in accurate expression, perhaps more often it is due rather to imperfect understanding. Perhaps we all have a more or less

clear mental picture of shock, yet occasions arise when it is by no means simple to make a confident diagnosis. Internal hæmorrhage or cardio-vascular accidents may simulate true shock, as pointed out by Virgil H. Moon in an article on the subject.[1] He refers to the well-known report of the special committee of the Medical Research Council in 1919, in which the extensive material available under conditions of war was utilized, and from this he formulates this comprehensive definition. "Shock is a circulatory deficiency, not cardiac or vasomotor in origin, characterized by a decreased volume of blood and cardiac output and by hæmoconcentration." The alteration in blood concentration he regards as specially useful as an indicator of shock. With these conditions are associated also such features as lowered blood pressure and basal metabolism, diminution of renal excretion and an increase in the rate of the heart, which are not of themselves pathognomonic, but, taken with the state described in the definition, are quite distinctive. Moon points out that many other allied features may be observed which are not constant concomitants of shock, such as a decrease in the alkali reserve, variations in temperature and in respiration rate, vomiting, diarrhœa *et cetera*. The autopsy findings are more or less characteristic. The superficial veins are flat and bloodless, and the blood is dark and fluid; the serous surfaces are congested and perhaps ecchymotic; the lungs and kidneys show intense congestion, and microscopic examination of the tissues reveals capillary hæmorrhages and considerable œdema. The spleen is small and contracted, and the heart is engorged and cyanotic. The condition of the adrenal glands is of some interest on account of the strong resemblance of the syndrome of shock to the symptoms observed after extirpation of these glands. They are greatly congested and the cells of the cortex frequently show vacuolation. Adenal disturbance cannot be the prime cause of shock, however; Moon points out that symptoms like shock do not arise after adrenalectomy until several days have elapsed.

Returning to the original report of the Medical Research Council, several important facts then established must be noted. It was shown that the circulatory failure of shock is not due to cardiac or to vasomotor inefficiency, for the heart is able to maintain an adequate blood pressure if supplied with fluid, and the peripheral arteries are not in a state of atony, but show active contraction. But here is seen the relevance of the hypothesis of an altered permeability of the venules and capillaries. This allows a proportion of the body fluids to be wasted so far as an active circulation is concerned, and the clinical and pathological pictures correspond very well. That the liberation of a histamine-like substance is concerned in causing this seepage of œdema fluids into the tissues, and their congestion, is not suggested as the standard mechanism in all cases, for, as Moon remarks, shock is an entity that may arise from various sources.

As regards the more practical consideration of diagnosis, there are some useful points to consider. In hæmorrhage the concentration of the blood is at first unchanged, though it will soon be lowered, owing to passage of tissue fluid into the blood vessels; in shock the lowered blood concentration is a very early sign. Of course shock and hæmorrhage may occur together, as in severe accidents. Syncope is a more transient condition; in syncope no qualitative changes occur either in the blood or in the walls of the capillaries, and here again there is no disturbance of hæmoconcentration. Less simple is the differentiation of shock from some sudden vascular accident, such as coronary occlusion. The clinical features are usually distinctive, but it should be noted that a purely passive congestion, an early feature of most intrinsic failures of circulation, is not observed in shock. This distinction is one that concerns the pathologist rather than the clinician, and is not of much help at the bedside. But Moon emphasizes that death is not actually due to heart failure in shock; he prefers some term such as "acute venous congestion", for the visceral engorgement found *post mortem* is not cardiac.

Great interest was taken in the subject of shock during the World War; the subject has been studied intensively since by many workers, but perhaps clinical interest in the exact mechanism has somewhat faded. For this reason it is useful to draw attention to what is implied in the word "shock", for clearer understanding must be of practical value.

[1] *Archives of Pathology*, September, 1936.

PROTAMINE ZINC INSULIN.

IT is known that the action of insulin in animals may be prolonged by the addition to it of zinc, and that the same phenomenon is seen in the case of Hagedorn's protamine zinc insulin when employed upon the human diabetic. I. M. Rabinowitch, A. F. Fowler and A. C. Corcoran[1] have now presented a lengthy and important paper dealing with their observations upon 132 diabetics treated with this form of insulin. The first point of importance which the authors stress is that hypoglycæmic reactions are rare in patients treated with this agent, and this although there is a reduction of the blood sugar below the hypoglycæmic level. It would appear that in these circumstances some mechanism is stimulated which again raises the blood sugar to its normal height. Blood pressure and blood sugar readings indicate that there is an antagonistic relationship between the two hormones, insulin and epinephrine; and it is suggested that the rise in blood sugar is brought about by the latter of the two. The infrequency of hypoglycæmic reactions in diabetics treated with protamine insulin or protamine zinc insulin may therefore follow the setting free of epinephrine at greater speed than that at which insulin is liberated from the protamine combination. The observed absence of signs

[1] *The Canadian Medical Association Journal*, February, 1937.

of hypoglycæmia in these cases may indicate that the blood sugar concentration is not a true index of the glucose concentration in the general body tissues.

Although there have been adverse reports upon the stability of protamine zinc insulin, the authors here cited maintain that its activity will remain unchanged even if it be kept for six months at room temperature. They admit, however, that the contradictory opinions of other workers are an argument in favour of the standardization of the product.

Several precautions must be taken when insulin in this form is used. It is a protein mixture and must therefore not be shaken violently to secure uniform suspension, nor must alcohol be used for purposes of sterilization unless removed from both syringe and needle before injections are given. Moreover, the mixture depends for its efficiency upon an accurately adjusted pH, which means that separate instruments and separate sites of injection must be employed to prevent the possible contamination of protamine zinc insulin with the unmodified form. Again, the sterilization of syringes in common tap-water leads to the deposition in them of alkaline carbonates, which are active solvents of protein and protein precipitates, so that the periodical use of dilute hydrochloric acid is necessary.

As the benefit of protamine zinc insulin is believed, with good reason, to reside in its capacity to liberate insulin at a slow rate, a state of grave acidosis would appear to be a contraindication to its use; that this is not necessarily so is shown by a rapid decrease in blood sugar after the injection of a large initial dose. Strangely enough, however, 100 units of the product have no greater effect in lowering the blood sugar than have fifty, though there is a difference in the speed with which the figures reach normal levels in the two cases. If the dose is sufficiently great, the blood sugar may sink below the normal level, to remain at that level for the space of thirty-six hours or more. Patients given gradually increasing amounts of food, on the so-called "ladder diet" plan, have responded very satisfactorily to the use of protamine zinc insulin. Judging from their blood sugar readings, their response was not only better than that to unmodified insulin, but the improvement was generally brought about by the employment of only one injection per day. Rabinowitch and his co-workers do not view favourably the practice of frequent estimation of the blood sugar during treatment with this form of insulin. They consider that it complicates treatment and may unnecessarily irritate the patient. They are content to believe that, with few easily detected exceptions, a twenty-four hour sample of urine free of sugar is an excellent indication that the blood sugar during that twenty-four hours has been at the normal level.

In general, the authors state, moderately severe diabetes may be controlled by single large doses of protamine zinc insulin given at twenty-four hour intervals, and its action not infrequently continues for at least thirty-six hours. This statement is the fruit of their observations of adult and juvenile patients with diabetes of all grades of severity. Amongst 132 cases of diabetes, eight failures are cited. In these, the control of the glycosuria in diabetics with normal renal thresholds was not achieved, or the blood sugar could not be brought to normal in the fasting state when hyperglycæmia existed in the absence of glycosuria. Excluding these eight patients, there were but three to whom it was found necessary to administer more than one injection per day. The excellence of these results is attributed to the uniform potency of the product used by the authors, to the precautions, previously outlined, which were employed to prevent its deterioration, to the selection of patients who would cooperate in treatment, and to the fact that all patients were kept under observation in hospital. In a forthcoming study these three workers hope to announce the results of their work with this variety of insulin upon diabetics suffering from surgical complications. A preliminary report from, with one exception, the same group of investigators lends colour to the belief that an improvement had been made in the treatment of diabetics. It is likely that protamine zinc insulin will shortly be made available for general use, when the advantages claimed for it—lasting effects, small dosage and need for fewer injections—can be corroborated. So far, the use of the product seems to require very careful supervision of the diet and the dosage, as well as hospital control of patients.

THROMBO-ANGIITIS OBLITERANS.

In the year 1924, Buerger published an excellent account of the disease which bears his name, and, although other observers had previously described the condition, alternatively known as *thrombo-angiitis obliterans*, part of the importance of Buerger's work lay in the fact that he first noted that the condition was not confined to arteries alone, but was in a considerable percentage of cases accompanied by phlebitis.

Emeritus Professor E. D. Telford[1] has now furnished us with a succinct and well-documented account of this disease, which must be regarded as one of the most important contributions on the subject during late years. Characteristically, the disease commences in the medium-sized vessels of the limbs, extending upwards and downwards, with intervening healthy patches. The vessels of the upper extremities are rarely affected, but the lesions have been discovered in the spermatic and mesenteric arteries. The duration of the disease is subject to the widest variations; one patient suffered from it for thirty-eight years, while a second died seven months after the onset of claudication. The influence of sex is truly remarkable; Buerger himself discovered only three instances of thrombo-

[1] *The Lancet*, March 6, 1937.

angiitis amongst women in 500 cases, and this is roughly the usual incidence. The origin of the malady, the common immunity of women and the reasons for its predilection for the lower limbs are as yet unexplained.

The traditional belief that *thrombo-angiitis obliterans* is commoner amongst the Jewish than other races has now apparently to be abandoned. Statistically it would seem that the Jew suffers from the disease in the same ratio as other men, and during recent years large numbers of cases have been reported from China and Siam. The age incidence is heaviest in the thirty to forty year period, but in one remarkable instance a boy of eight years was a victim, and by the age of nineteen he had lost from gangrene half of one foot and all the toes of the other. On one point there is general agreement—that of the histo-pathology. First, there is a stealthy lymphocytic invasion of the arterial and venous coats. Next, clotting occurs within the vessels and the clots undergo organization, with a resulting fibrosis. At the same time extravascular fibrosis ends in the formation of formidable masses of fibrous tissue, impossible of dissection and containing the now completely solid vessels.

As yet the prime causes of this strange disease are unknown. There is no relationship between it and syphilis. Regarding the use of tobacco, it is apparent that while many sufferers are heavy smokers, cases are frequently seen in persons who have never used tobacco in their lives. The disease is likely to afflict men of good physique and of athletic habit, and especially those who, while engaged in heavy physical work, have been exposed to wet and cold. No helpful clues as to causation have as yet been discovered on examination of the blood for calcium, phosphorus, sugar or urea. The blood coagulation time is usually normal. If the underlying cause of the disease is to be found in vascular spasticity, the operation of sympathectomy might be supposed to be a useful measure of alleviation; if, on the other hand, a toxic or infective factor is involved, this operation could only result in improvement by producing a dilatation of vascular paths still remaining healthy. Colour is lent to the view that the disease may be toxic in origin, however, by the observation that the onset of arterial changes is sometimes preceded by phlebitis.

The signs and symptoms of the disease include coldness of the feet, claudication during slight exercise, severe pains in the calves or feet, loss of arterial pulse, and trophic changes, usually in relation to the nails of the great toes, which may later proceed to a terminal and spreading gangrene. The diagnosis, which may be made with some confidence amongst patients between forty-five and fifty years of age, is probably incorrect in those past the sixth decade. Many sufferers from thrombo-angiitis have in the past been adjudged to require treatment for fibrositis, chronic rheumatism or flat-feet. The presence of calcification, as revealed by skiagrams, in the vessels of a suspected limb, immediately relegates the case to the arterio-sclerotic group, since deposits of lime do not occur during the course of *thrombo-angiitis obliterans*.

Treatment by physical therapy and by injections of foreign proteins have no more than a temporary and palliative effect. Up to the present, surgical methods have offered the only chance of lasting benefit, and this whether the disease is of spastic or toxic origin. The operation recommended by Telford may take the form of either perivascular stripping or of lumbar cord ganglionectomy. The results of the latter operation are classed as good in half of Telford's recorded cases; in the remainder the clinical results were fair only, but in certain instances seemed to permit of secondary amputations of less gravity than might otherwise have been necessary. It is well to remember that A. E. Coates, of Melbourne, writing in this journal, is emphatic that periarterial stripping is of no value in this condition, and that ganglionectomy is the surest means of depriving arteries of their vaso-constrictor fibres. Coates also holds, and we think rightly, that if it is obvious that amputation will be necessary, it is not justifiable to subject a patient to the major operation of sympathetic ganglionectomy.

Telford makes no mention of the fact, previously recorded in 1934 by G. E. Brown, that the pain of trophic ulcers may be greatly lessened by the alcoholic blocking of sensory nerves. G. W. Pickering has also pointed out the value of Pachon's oscillometer in confirming the presence or absence of arterial pulsation in arteries, such as those of the calf of the leg, which lie too deep for palpation.

DERMATOMYOSITIS.

L. J. WITTS recently reported to the Section of Dermatology of the Royal Society of Medicine a case of dermatomyositis occurring in a boy, aged fourteen years.[1] The condition was at first mistaken for a severe sunburn; but then signs of a general toxæmia appeared. The characteristic dermatitis involved the face, arms, buttocks and thighs, but not the trunk. There was weakness of the skeletal muscles, including those of the palate and pharynx, but excluding the laryngeal and ocular muscles. The muscles had not been swollen, but felt rigid, and limitation of movement was present. Witts said that biopsy revealed the changes of dermatomyositis in skin and muscles. In the discussion, J. T. Ingram referred to the literature of dermatomyositis and of poikilodermia Jacobi; he thought that the two conditions were related. G. B. Dowling referred to this relationship and to the differences in the histological picture of the two conditions. In the poikilodermia of Jacobi there were always nodules of dense cellular infiltration immediately beneath the dermis, to be seen clinically as tiny papules. This infiltration was not seen in dermatomyositis, and in no case of poikilodermia Jacobi had there been evidence of serious muscle disease.

[1] *Proceedings of the Royal Society of Medicine*, August, 1936.

Abstracts from Current Medical Literature.

MORBID ANATOMY.

Supravital Staining of Leucocytes in Normal and Leuchæmic Blood.

L. E. H. WHITBY AND M. HYNES (*The Journal of Pathology and Bacteriology*, July, 1936) have carried out examinations of the leucocytes of normal and leuchæmic blood by the supravital staining methods of Sabin and Doan. They describe the technique fully and emphasize the necessity for purity of solutions, cleanliness of glassware, and the exclusion of light, except when the preparations are actually being examined. The stains used are neutral red for the demonstration of granules in mature myeloid cells, and the filling of vacuoles, and Janus green for the staining of mitochondria. The preparations are examined on a warm stage, and an unstained preparation is used as a control of the motility of the normal leucocytes, in which the nucleus and cytoplasm of the leucocytes must be completely unstained. The erythrocyte is a clear yellow, and 1% contains a dull red granule which does not appear to compare with the reticular material. The neutrophile cell is active, moving 3μ per minute, and it has a large number of fine yellow granules and few vacuoles. It moves constantly in one direction, and the putting forth of irregular pseudopodia is a sign of ill-health. The eosinophile cell has large oat-shaped granules, its movement is more sluggish. The basophile cell is of amœboid shape when cold and has deep maroon granules. The lymphocyte has a circular outline, a circular nucleus, and numerous mitochondria grouped in rows or to one side of the nucleus. Two to five bright red vacuoles are usually present. The monocyte has a U-shaped nucleus, the mitochondria are scattered, there are numerous red vacuoles which may appear as a rosette in the "hof" of the nucleus. Motility is slight. The myeloblast is a round non-motile cell almost filled by the nucleus. Mitochondria are very fine, and no structures stained by neutral red are present. Myelocytes are described according to Sabin's three forms. "A" form has one to ten brownish granules. "B" and "C" have large numbers of granules; the cells are larger and more mature. Myelocyte "C" is nearest to the adult form, with fewer mitochondria. There is streaming of the granules and even sluggish movement. The lymphoblast is a round, non-motile cell with a central nucleus and large oval mitochondria. Maturation of the cell is indicated by bright red vacuoles. Monocytes are very large in immaturity, with sluggish movement. The nucleus is always in the rear of the cell. The mitochondria are fine and there are many orange-red vacuoles. Erythroblasts are non-motile, with an eccentric nucleus, showing definite bands of chromatin. Few fine mitochondria are present, and sometimes coarse vacuoles. Normoblasts have a structureless nucleus, few vacuoles and infrequent mitochondria. The technique of supravital staining is described as simple and the interpretation as relatively easy. The significance of the vacuolar bodies is unknown, as there is no corresponding structure in stained preparations. The authors note the increased motility in certain diseased states, such as eosinophilic leuchæmia, in which the eosinophile cells are as active as the normal granular cell. The method does not throw any light on the origin of the monocyte, but seems to indicate its close origin relation with the granular cell. The existence of a true monocytic leuchæmia is undoubted, and the possibility of a mixed type is suggested and discussed.

Benign Enlargement of the Prostate in the Dog.

THE changes induced by œstrogens in the male reproductive organs of laboratory mammals have suggested that spontaneous prostatic enlargement in man results from the prolonged œstrogenic stimulation of the prostate, following a primary imbalance between "male" hormone and some œstrogenic agent also elaborated in the male organism. S. Zuckerman and J. R. Groome (*The Journal of Pathology and Bacteriology*, January, 1937) have studied the prostates of nine mature dogs. Only one was normal. Seven of the remaining eight were enlarged; the enlargement was due to hyperplasia. The authors state that if the normal activity of the prostate is under the control of male hormone, as is generally believed, it is conceivable that this kind of enlargement is due to an excess of male hormone. The ninth prostate was greatly and irregularly enlarged. Its histological structure was different from that of the other enlarged specimens. In this instance enlargement was due to excessive and unceasing division of cells derived from the epithelium of the urogenital sinus. These changes are identical with those produced experimentally by the introduction of œstrogens. It is concluded that in this instance the enlargement was a response to an œstrogenic agent elaborated within the animal's body. The finding is regarded as direct evidence that enlargement of the prostate may result spontaneously from an excess of œstrogenic stimulation.

Familial Hæmorrhagic Telangiectasia.

NORAH H. SCHUSTER (*The Journal of Pathology and Bacteriology*, January, 1937) reports a case of familial hæmorrhagic telangiectasia associated with multiple aneurysms of the splenic artery. She points out that the literature on this condition is quite extensive, but that it is confused by the inclusion of other hæmorrhagic diseases. Twenty fatal cases have been recorded, and in these instances death usually resulted from hæmorrhage or anæmia. In the case described by the author a *post mortem* examination was made and the organs were studied microscopically. She points out that the patient died in a late stage of the illness and exhibited so many lesions that were obviously not associated with one another, that it is "unprofitable to speculate on the sequence of events". The patient, a woman, aged sixty-two years at the time of her death, was under observation for fourteen years before she died. She suffered for many years from epistaxis; she also suffered from intermittent hæmorrhages from various other sources and had many cutaneous telangiectases, which tended to occur in crops at intervals of a few months. She finally died of bronchopneumonia and cardiac failure. Telangiectases were present in the skin, nose, mouth, pharynx, larynx, trachea, stomach and duodenum. They were not present in the bronchi, colon, rectum, kidneys or serous membranes. The author applies the term telangiectasis promiscuously to all small red or purplish spots, flat or raised, due to the presence of dilated blood vessels. The author adds that it has always been disputed whether the skin lesions are vascular neoplasms or simple dilatations. She considers that they have no special structure that distinguishes them from telangiectases occurring in other pathological states. There were also found abnormalities of arteries and veins (the splenic artery was the site of many aneurysms) and these are regarded as being congenital developmental defects.

Vitamin B Deficiency.

CHARLES DAVISON AND LEO STONE (*Archives of Pathology*, February, 1937) find that when diets deficient in vitamin B_1 or in vitamins B_1 and B_2 are given to rats, there occur such neurological signs as dragging and paralysis of the extremities, equilibratory disturbances, priapism, convulsions and tonic retraction of the head. Pathologically the outstanding picture is that of disintegration of the myelin sheaths of the peripheral nerves and vacuolation and liquefaction necrosis of the ganglion cells of the mesencephalon, metencephalon and anterior horns of the spinal cord. Hæmorrhages, with changes in the ganglion and glia cells of the mesencephalon, are also encountered in animals with convulsions.

Blood and Cancer in Mice.

L. C. STRONG AND L. D. FRANCIS (*Archives of Pathology*, February, 1937) have made a study of the blood of two inbred strains of female mice. One strain was cancer-susceptible, the other cancer-resistant. The blood of the former had a significantly lower level of hæmoglobin and total protein than that of the latter.

MORPHOLOGY.

Ossa Suprasternalia.

W. MONTAGUE COBB (*Journal of Anatomy*, January, 1937) describes an investigation on the variation and incidence of suprasternal bones and the form of the superior manubrial border in 2,204 human and 107 anthropoid sterna. The suprasternal bones originate in lateral condensations of mesoderm from the median *Anlage* of the sternum. The *Anlagen* become cartilaginous. The cartilaginous stage has been noted at six fœtal months and may persist into adult life. Ossification, partial or complete, generally occurs between the ages of seventeen and twenty-three. The ossicles appear to be rudiments of the epicoracoids of the primitive shoulder girdle. They range in size between that of a small shot and an average female lunate bone. Their structure is similar to that of the sternum, consisting of a cancellous tissue surrounded by a thin layer of compactum. Ossicles of all types occupy a constant position on the posterior manubrial border adjoining and many times confluent with the clavicular articular surfaces. They occur in pairs or singly. They may be separate, forming a diarthrodial joint with the manubrium; they may be united to the manubrium by synchrondrosis; or as small nodules they may be ensconced within the suprasternal ligaments and have no contact with the manubrium. The superior manubrial border may be convex, straight or concave. The human sternum, with convex manubrial border and well-developed separate ossicles, retains the greatest number and quantity of primitive shoulder girdle elements and must be considered the primitive type, while the markedly concave sternum represents the greatest reduction in primitive elements and is hence the most advanced. Convex and straight manubrial borders occur in greater proportion in whites than in negroes. This fact, coupled with the greater incidence of ossicles of all types and the greater proportion of separate ossicles in the whites, seems to indicate that the negro has progressed further than the white in simplification of the upper end of the presternum. The distance along the superior manubrial border, between the claviculo-articular surfaces, has a greater tendency to be wide relative to the breadth of the manubrium in males than in females. In the anthropoid series no suprasternal ossicles or tubercles were found, but their superior manubrial border was classified in the same way as the human.

Abdominal Vagal Paraganglia.

IN an article by N. Goormaghtigh (*Journal of Anatomy*, October, 1936) the existence in the adult mouse of abdominal vagal paraganglia, distinguishable from the sympathetic paraganglia, is demonstrated. The vagal paraganglia are embedded in or adherent to different branches of the abdominal vagus. Their distinctive features, as opposed to those of sympathetic paraganglia, consist in the absence of a chromaffin reaction and in the smaller size of the cells, which are grouped in ellipsoidal compact bodies. The author discusses the question of whether the abdominal paraganglia are connected with the sensory or motor constituents of the abdominal vagus. He believes there is no evidence in favour of the idea that the abdominal vagal paraganglionic complexes have the same physiological significance as the vagal paraganglionic complexes of the aortic and carotid regions. He concludes that there is no evidence of the sensory nature of these paraganglia. There is more reason to believe that they are a glandular annex to the efferent fibres of the vagus. As to the nature of the eventual chemical substance produced by them, the possibility of an acetyletroline secretion is put forward on the evidence provided by recent physiological research.

Early Human Ovum.

P. N. B. ODGERS (*Journal of Anatomy*, January, 1937) describes an early human ovum which he proposes to call the Thomson ovum. The interior measurements of the blastocyst cavity are 2·1 by 1·51 by 0·7 millimetres. Its maximal age is about sixteen days. The extraembryonic cœlom is seen to be commencing as fairly symmetrical channels on either side of the amnio-embryonic vesicle. A comparable appearance to this has been observed previously only in the Peters and Tennant-Ramsey ova. The yolk sac has a lining of cubical entoderm beneath the disk; elsewhere it is merely outlined by a sparse layer of spindle-shaped mesothelial-like cells. This condition is shown not to be exceptional in the earlier ova, and is held to corroborate Stieve's conception of an entodermal plate spreading ventrally to form the proper entodermal wall of the yolk sac as seen in later embryos.

Ectopia of the Kidney.

A CASE of crossed ectopia of the kidney in an aged male dissecting room subject is described by Alice Carleton (*Journal of Anatomy*, January, 1937) and a theory is put forward to account for anomalies of renal fusion. They occur, it is suggested, between the five and eight millimetre stages. A crossed ectopic kidney arises when fusion occurs between developing masses which show an unusually high degree of difference in growth rate. Should the cells round the lower diverticulum of one ureteric bud unite with those round the upper diverticulum of the other, an end-to-end or overlapping fusion will result. Direct median ascent is barred by the vessels passing to the gut. The mass must therefore grow up on one side or the other. In the majority of cases the upper kidney leads the way to its own side. When the reverse happens, it might be due to an asymmetrical union, so that ascent on the side of the lower kidney offered less obstruction. All grades of ascent have been found, and the lower kidney may never cross the midline completely, but may remain centrally placed on or below the pelvic brim. This has been called a sigmoid variety of horseshoe kidney, but is more truly a crossed ectopic kidney which has failed to complete its crossing. If the metanephric masses are at the same level when fusion occurs, the result is a horseshoe or cake kidney, depending on the extent of fusion. Abnormalities of origin of the umbilical arteries might provide the primary cause of renal fusion. A summary of the findings in previous cases is included.

Vascularization of the Opossum's Brain.

AN unusual pattern of the blood vessels supplying the brain and cord of the opossum (*Didelphys virginiana*) is recorded by G. B. Wislocki and A. C. P. Campbell (*Anatomical Record*, January, 1937). The blood vessels enter the substance of the brain and cord in pairs, consisting of an artery and a vein. These continue to branch in pairs down to and including the capillaries, which consist of thread-like terminal loops. Neither the paired vessels nor the terminal capillaries anastomose with other similar vessels. The brain is supplied consequently by distinct and separate vascular units, which do not anastomose with one another. These units consist of end arteries in the sense of Cohnheim, with the additional feature that the ultimate capillaries are also end vessels. Although the capillaries of adjacent systems do not unite, the capillary loops of contiguous units interdigitate freely. The opossum is the only mammal so far examined in which a vascular pattern of this nature has been observed. It has been described before in lizards and in some urodele amphibians. In some insectivores, ungulates, rodents, carnivores and bats, also in the armadillo, rhesus monkey and in man, the capillary bed is known to be of the network type. Capillary networks have also been observed in fishes, anuran amphibia, snakes, tortoises, crocodiles and birds.

Proprioceptor Fibres from the Tongue.

DONALD H. BARRON (*Anatomical Record*, August, 1936) concludes that the lingual, and not the hypoglossal nerve, contains the sensory fibres which conduct proprioceptive sensation into the brain stem from the tongue. The cell bodies of these fibres are to be found either in the Gasserian ganglion or in the brain stem in association with those of the fibres carrying proprioceptive impulses from the muscles of mastication.

Special Abstract.

LEPTOSPIROSIS IN JAPAN.

IN Japan there occur three varieties of leptospirosis. They are, in descending order of severity, Weil's disease, autumn fever and seven-day fever. They have many features in common, and milder cases especially may be difficult to classify. The main differences may be roughly summarized as in the accompanying table.

Condition.	Species of Spirochæte.	Jaundice.	Mortality.
Weil's disease	*Leptospira icterohæmorrhagiæ.*	Frequent.	Appreciable, 5% to 30%.
Autumn fever (Akiyami, Hasamiyami).	*Leptospira autumnalis.*	Frequent.	Low.
Seven-day fever (Nanukayami).	*Leptospira hebdomadis.*	Does not occur.	Nil.

The existence in Queensland of at least three kinds of leptospirosis invites comparison with the position in Japan. Weil's disease is frequently reported in the overseas journals. Seven-day fever is described elsewhere in this issue. The following summary of the clinical aspects of autumn fever is taken from an article by Saigo Kotorii published in the *Klinische Wochenschrift* of August 10, 1935, page 1147. The article has been translated by Dr. E. H. Derrick, of Brisbane, who has been good enough to forward it for publication.

Attention may be called to certain outstanding points in the description: the strict limitation of the disease to one period of the year, its occupational nature, the high incidence of jaundice, yet with a low mortality, and the peculiar sequel of clouding of the vitreous, which has not so far been recorded as occurring in the leptospiroses of Australia.

Dr. Kotorii has studied this disease for thirty-two years, both clinically and in the laboratory. He also had the misfortune in 1933 to infect himself accidentally with a mouth pipette, and underwent a severe attack. He is therefore well qualified to speak authoritatively.

In the district of Hasami, in the province of Nagasaki, there occurs an endemic disease resembling Weil's disease. Kotorii writes that in the course of thirty-two years he has reported on it as para-Weil's disease, as *nanukayami* (seven-day fever) and at times as a new spirochætosis intermediate between these two. In 1931 this disease (Kotorii refers to it as *hasamiyami*) was established by Professor Abe and his co-workers, including Kotorii, as ætiologically identical with *akiyami*, or autumn fever, a spirochætosis due to the *Spirochæta autumnalis*.

Epidemiological Considerations.

The town of Hasami, which consists chiefly of rice fields, and is a well-known rice production area, lies in the northerly part of the prefecture of Nagasaki, on the bank of the River Kawatana, surrounded on three sides by mountains which open only to the south. The River Kawatana runs slowly through the town of Hasami and the more southerly situated town of Kawatana, and flows into Sonogi Bay. The inhabitants number about 12,000; they are chiefly employed in agriculture, in part also in porcelain burning.

The number of *hasamiyami* patients treated in Kotorii's private practice in thirty-two years (1903 to 1934) has amounted to 418. He sets out the figures for the several years in a table.

The cases of *hasamiyami* have been scattered throughout the town. There exists no pronounced relation between the hygienic condition of the dwelling, whether it is damp or sunny, or the position of the house, whether it is situated in mountain, field or street, and the occurrence of the disease.

The 418 *hasamiyami* patients comprised 291 (69·6%) males and 127 (30·4%) females. By far the largest number of patients was found in the age groups 11 and 20, and 21 and 30.

Contact infection (perhaps through lactation) was observed in the case of an infant of one year and five months. The mother suffered from *hasamiyami* from September 7, 1922, on. The child, which was still on the breast, took ill suddenly on the morning of September 21 with fever, followed by convulsions and then lethargy. There was some vomiting. The fever continued till September 25. On September 27 jaundice appeared and petechiæ in the skin of the breast and abdomen. On September 30 the child was fever-free.

The disease attacked chiefly farmers who worked in the fields and took their wives and children with them. Kotorii thinks that most probably the infection enters mainly through the skin. It is possible that any wounded place (injuries or cracks in the skin or mucous membrane) may serve as a site of entry, because the farmer in this district mostly works with bare feet.

Contact infection of those who care for the sick is apparently extremely rare.

Whether the infecting agent can also be transmitted *per os*, Kotorii cannot say with certainty, while experimental confirmation is lacking; but he thinks that it may be accepted on the evidence of his observation of the above-mentioned infant and a case of laboratory infection reported by Honda and himself.

The incidence of this infection is strictly limited to the end of summer and the beginning of autumn, and it reaches its maximum in September.

In the course of thirty-two years Kotorii has experienced only nine cases of reinfection.

Symptomatology.

The incubation period is five to fifteen days. The disease usually runs its course without special features; sometimes there are headache, languor and poorness of appetite.

Kotorii based his estimate of the length of the incubation period on the following observations: (*a*) Three porcelain dealers went fishing together in the river and all became ill after ten, eleven and twelve days. (*b*) A schoolboy became ill five days after standing once only in slimy water. (*c*) A housewife and her mother, who usually worked in the house, were attacked by this fever after eight days' work in the rice field. (*d*) An infant with the housewife and mother became infected after a period of fifteen days.

As a rule the illness begins suddenly without prodromal symptoms. The patient has repeated shivers, high fever, headache, pains in the muscles and loss of appetite. The muscle pains set in somewhat later. They are in general so violent that the victims can hardly stand up. The fever remains continuously high for three to five days, then falls gradually by lysis within two or three days. With a normal course, apart from complications, such as bronchopneumonia, parotitis *et cetera*, the fever period never lasts longer than ten days; there is no secondary fever, as with Weil's disease. In addition to these symptoms, jaundice comes on in about half the cases as the fever falls. A sequel in most cases is clouding of the vitreous.

Digestive Organs.—At the beginning the tongue is dry and coated grey-white or dirty black; it is often cracked. The lips are usually quite dry and cracked, especially at the angles of the mouth. *Herpes labialis* is found in few cases. Inflammation of the throat is often observed (sub-

jectively as dysphagia, objectively as redness and swelling), especially at the onset. Loss of appetite is a most regular feature. A feeling of fullness and tenderness in the epigastrium, nausea and vomiting are fairly frequent. Diarrhœa is not characteristic; constipation is often seen. The stools are as a rule like soup, and yellowish, clay-coloured, not silver-grey, and in severe cases are often mixed with blood. The liver is palpable in 80% of cases; the enlargement is often observable by the second and third day of the illness. The spleen is much more rarely palpable.

The Appearance of the Skin.—Icterus occurred in 198 of the 418 cases, that is 47·4%. Its intensity runs largely parallel with the severity of the illness. It sets in as a rule on the fourth to the sixth day of illness, reaches its maximum some days after the fall of the fever, and then fades gradually away within seven to ten days. A tendency to bleeding was indicated by petechiæ and ecchymoses of the skin in 9·6% and by epistaxis in 4·5% of cases. The bleeding was limited mostly to highly jaundiced cases. With female patients there was occasionally bleeding from the uterus. An exanthem of urticarial type was observed in one case only.

Respiratory System.—Bronchial catarrh occurs often; and in severe cases bronchopneumonia occasionally complicates and prolongs the illness.

Circulatory System.—At the outset the pulse rate is frequent (100 to 130); the vessel is readily compressible. With the onset of icterus the pulse rate returns to normal. The heart at first is strongly accelerated and the sounds are accentuated. There is often a systolic murmur at the apex. Heart weakness associated with arrhythmia is rare and occurs only in severe cases at the period of slowing of the pulse.

Blood Picture.—In the blood Kotorii reported that Amenemori had found a leucocytosis with polynucleosis and lymphocytosis at the beginning of the illness, and later a change to relative lymphopenia. Large monocytes and transition forms, at the beginning 3%, increase gradually to 12·5%. Eosinophilia is found only in the early stage. Basophile leucocytes are not to be seen throughout. The erythrocytes and the hæmoglobin contents show no peculiarity.

The Urine.—The urine in the febrile period is cloudy and yellowish-brown in colour. The reaction is strongly acid, the specific gravity is increased. Albumin is present more or less in all cases by the third or fifth day. The amount of bile pigment in typical cases is considerable. Epithelial cells and casts are found when the illness is severe. The quantity of urine is in general much decreased.

Nervous System.—Headache is a characteristic feature of this fever. Sleep is usually disturbed. Partial deafness, tinnitus, delirium and convulsions (in children) often develop with a severe attack.

The Eyes.—The majority of patients show almost as a rule a distinct hyperæmia of the conjunctiva, which is visible at the onset and which gradually passes off after one or two weeks. The grade of hyperæmia is usually more intense in the eyes than on the face, so that, seen from a distance, the vessels of the conjunctiva appear as if they had been treated with red cosmetic. There are no complaints of pains, but photophobia and watering of the eyes occur. Inflammations of the iris and ciliary body are very rare. Clouding of the vitreous occurs.

Muscle Pains.—Pains in the muscles, especially in the calf muscles, which are one of the pathognomonic signs of this disease, are usually so violent that the patients can scarcely change their position in the bed. The pains affect also the muscles of the thighs, loins, forearms, trunk and the back of the neck. It is obvious and noteworthy that the pains occur in the muscle groups usually used most; in labourers, next after the calf muscles those of the loins and thighs are affected; in those who follow other occupations, after the calf muscles those of the neck, breast and abdomen are involved. Muscle pains are already present as a rule on the third day of the illness and remain throughout the whole fever period. Joint pains do not occur.

Gland Swellings.—Swellings of the glands occur in about 20% of cases, not including the slight swellings of the submental glands that are associated with bronchitis. The most frequently enlarged are the inguinal, axillary, cubital and cervical glands. The swollen glands are from the size of a pea to that of a broad bean, and are elastic and tender to pressure.

Complications.

Complications are infrequent, but bronchopneumonia (1·7%), *herpes labialis* (2·6%) and parotitis (1·4%) may be cited.

Sequelæ.

As a sequel, clouding of the vitreous is met with almost constantly. It usually occurs one to two months after recovery, but occasionally early in the course of the illness or six to twelve months later. The clouding sets in with scintillation (*Flimmerschen*), with or without interference with vision. The vitreous presents a coarse, irregularly shaped, dust-like appearance, not like the fine misty appearance of a syphilitic clouding. The grade of the eye symptoms does not always correspond to the grade of the general condition. Kotorii states that he cannot determine how often vitreous clouding arises, because the mild forms run a very favourable course and clearing follows without treatment. If a thorough ophthalmological investigation were made, it would, he thinks, be found to occur in about 90% of cases. Iritis, uveitis and cataract are met with only in isolated cases.

About twenty days after the fever the hair quite often falls out, especially the hair of the head; the skin also may peel off. The nails become brittle and cracked; a border-line between the old and newly formed parts is frequently present and is to be seen quite clearly two months after the fever, especially with severe cases.

Prognosis.

The mortality of *hasamiyami* is low—1·9%. Of the 418 patients, only eight died; those who died were almost without exception men of over fifty years of age. If one estimates the mortality of only the 58 patients over fifty years of age, the percentage is 13·8. *Hasamiyami* is therefore rather dangerous for older men, but has a favourable prognosis in childhood and manhood. With old men, weakness and loss of appetite at the beginning of the illness are unfavourable prognostically; so is a temperature that does not rise particularly high.

Diagnosis.

In the autumn months the occurrence of a feverish disease with distinct hyperæmia of the conjunctiva and violent muscle pains should arouse suspicion of *hasamiyami*. In fact, fever, muscle pains and conjunctival hyperæmia are three cardinal symptoms of *hasamiyami*. But in mild cases without obvious hyperæmia and muscle pains it is difficult to differentiate this disease from a simple pharyngeal catarrh induced by a cold. In these cases increasing hyperæmia and muscle pains, exhaustion, and the constant occurrence of albuminuria are very important in establishing the diagnosis. Icterus also at times plays an important rôle. Catarrhal jaundice can be excluded by means of the above-mentioned three cardinal symptoms. The differentiation of *hasamiyami* with jaundice from catarrhal jaundice is easy if the previous history is thoroughly known and the condition of the patient's strength closely regarded. The leucocytosis is occasionally a good diagnostic help. The most certain way is the detection of the spirochætes in the blood.

British Medical Association News.

SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held at the Medical Society Hall, East Melbourne, on March 3, 1937, PROFESSOR R. MARSHALL ALLAN, the President, in the chair.

Symposium on Cancer.

The meeting took the form of a symposium on cancer.

The surgical aspect of the subject was presented by Sir Alan Newton. He said that the selection of cancer as the subject for discussion was doubtless dictated by the fact that an Anti-Cancer Council had recently been formed in Victoria and that an appeal to the public for funds to help it in its work was to be made in the following month. It was therefore eminently desirable that the Branch should debate the question of the most fruitful measures which should be taken by the Anti-Cancer Council when, by the acquisition of money, it was in a position to enter the fight against cancer. It was, of course, obvious that the discovery of the cause of cancer would be the first step in the solution of the problem of its effective treatment, and, to achieve this end, unstinted expenditure of work and of money was taking place in many centres of research throughout the world. Though the Victorian Anti-Cancer Council should encourage research work of this description if it should happen that a suitable worker required assistance, it seemed reasonable to suggest that it should direct its attention primarily to the task of fostering the treatment of patients suffering from cancer with the weapons at present available. Sir Alan Newton therefore proposed to confine his remarks to some aspects of the problem of the treatment of cancer, with special reference to improvements which might be effected by the Council.

The vast majority of sufferers from malignant disease were referred sooner or later to a surgeon, who was asked to give an opinion regarding the best method of treatment suitable for each individual case. In the case of sufferers from cancer of internal organs, the answer was generally easy, because unhappily the only hope lay in a successful surgical operation. If, owing to the extent of the disease, this was impossible, it might be possible to prolong life and to relieve suffering by a palliative operation. In the case of sufferers from cancer in accessible organs, such as the tongue, the lip or the breast, to mention only three types of case, the answer was not so easy, because the surgeon had to decide upon the relative merits of surgery and radiotherapy. The surgeon would necessarily be influenced first by the extent of the disease and, to a less degree, by a feeling of natural reluctance to advise an operation which must result in a permanent physical deformity. If the disease was too extensive to permit of removal, radiotherapy was the only hope. If this was not the case, he had to weigh the relative merits of these two forms of treatment. In the three types of cancer to which Sir Alan Newton had referred, cancer of the tongue, the lip and the breast, it had been customary for surgeons to refer patients suffering from cancer of the lip and the tongue to the radiotherapist and to advise surgical removal of the breast, despite the fact that there was a large body of opinion among radiotherapists that these patients also should be treated by them. It had been possible only recently to investigate the results of radium treatment of cancer in these situations, and the findings were somewhat disturbing. Searby had shown that radium had failed to cure any case of cancer of the tongue and that the result of this method of treatment was definitely worse than that obtained by surgeons prior to its introduction. McMahon, in an investigation of the results of radium treatment of cancer of the lip conducted in Sydney, had found that the results were not quite so good as the surgical results; and, finally, an investigation into the results of surgical treatment of carcinoma of the breast conducted by the Royal Australasian College of Surgeons two years previously, had demonstrated that, in operable cases, surgery afforded the best hope of cure. Sir Alan Newton said that he did not give these findings in any spirit of antagonism to radiotherapy. Indeed, he did not know what they would do without this method of alleviation in most cases and of cure in some cases of cancer. It might be that, with increased knowledge of its use, it would supplant surgery in the treatment of certain types of cancer. It might be that advances would be made in combining both methods of treatment. He did, however, wish to emphasize the fact that it was at present open to question whether surgeons should refer to the radiotherapist operable cases of cancer, even of such suitable areas for radiotherapy as the tongue and the lip. He had also to point out that it was unfortunate that, until recently, the cancer conferences at Canberra should have been almost exclusively confined to radiotherapists, for this necessarily gave rise to the impression in the minds of the public and of the profession that radiotherapy was the only modern method of treatment. The logical result of this position was that the Anti-Cancer Council in Victoria might suitably devote portion of its funds to a clinical investigation of the end results of different methods of the treatment of cancer, in order that surgeons might be helped in giving proper advice to their patients concerning the best type of treatment to be followed. Sir Alan Newton said that he would regard an investigation of this type as the most important contribution which could be made in Victoria.

Another somewhat similar type of investigation, of which there was an urgent need, was that of the late results of cases considered in relation to the pathological type of the growth. Every surgeon would agree that some types of cancer resisted any and every form of treatment, whereas other types, occurring in the same organ, could be easily cured by the means at present available. It was frequently difficult, at least in the early stages of the disease, to differentiate these various pathological types by clinical investigation. Sir Alan Newton was aware that much work had already been done in this direction, but he felt that it would be very helpful, from the surgical point of view, if it was possible to give a comparatively accurate prognosis after pathological examination of the growth. He had not been particularly impressed by the help given by pathologists in this direction, for it had been his experience that some growths, labelled very active, had failed to recur after removal, whereas others, described as slow-growing, had recurred rapidly. It therefore seemed desirable that the Anti-Cancer Council should institute what Sir Alan Newton thought he might be permitted to describe as a "pathological follow-up" of cancer cases.

Turning to another aspect of the question, Sir Alan Newton said that it had been suggested that it was necessary to take active steps to improve medical education in regard to malignant disease, and that all medical students should receive special education in those conditions grouped, for the purpose of this discussion, under the term "cancer". Such a suggestion could be construed only as a plea for better education of medical students, for everybody in practice would agree that the paramount difficulty consisted in the differential diagnosis of malignant from other conditions. This difficulty was emphasized in the classification of all swellings under one of the following headings: "acute inflammatory", "chronic inflammatory", "neoplastic" or "parasitic", with which all those present were familiar from their student days. It was quite impossible, and indeed wholely undesirable, to divorce cancer from all other conditions and to make a special subject of it from the diagnostic point of view. It had necessarily to be merged in the general stream of ward teaching relating to all pathological conditions. Sir Alan Newton took a similar attitude in regard to the treatment of cancer when an accurate diagnosis had been made, for this had to be considered in any given case, with due regard to the general physical condition of the patient, and therefore was inextricably mingled with many problems of general medicine and surgery. He did not believe, therefore, that it was necessary for the Council to advocate reforms of this nature in the undergraduate curriculum.

For similar reasons, Sir Alan Newton felt that so-called diagnostic centres in various country towns, which, as those present were aware, had been advocated, should comprise such adjuvants to clinical investigation as pathological laboratories and X ray facilities, rather than specially appointed clinicians for the purpose of diagnosis. It would surely be better to assist each family doctor to arrive at an accurate diagnosis by providing him with such facilities, than to remove his patients to another doctor in order that a diagnosis should be made. The Charities Board in Victoria was already taking steps to provide facilities of this type, so that it would probably be unnecessary for the Council to move in this direction.

Sir Alan Newton then referred to still another aspect of the proposed activities of the Council, that of public propaganda. There was no doubt that, unless great care was exercised, this would result in an enormous addition to the number of "cancerphobes" in Australia. Propaganda of this description, if adopted, should be confined to the hopeful aspects of the disease, particularly the efficacy of treatment. He felt that alarmist information about the increased frequency of cancer was to be deprecated, and he was sure that it would help in this direction if extracts from Dr. Cumpston's paper, read at the last cancer conference, were made public. It would be remembered that Dr. Cumpston had pointed out that the curve of deaths from senility was steadily falling, whilst the curve of deaths from malignant disease was rising in equal degree. Further, he had shown that there had been no increase in the incidence of malignant disease in young people.

Sir Alan Newton went on to say that in opening this discussion from the surgical standpoint he had made no reference so far to the results of surgical treatment of cancer, and those present would readily understand that, in the short time at his disposal it was impossible for him to deal with such a large question. He would therefore content himself with pointing out that his own experience, based on a fairly complete follow-up system of his patients, had led him to take a rather more optimistic view of the ultimate outlook for his patients than at one time he had thought would be possible. Failures were, of course, only too numerous, but even such an unfavourable group as those with gastric malignant disease showed an appreciable percentage of what were apparently permanent cures, while operative results in cancer of the breast and of the colon were surprisingly good.

In conclusion Sir Alan Newton said that he wished to emphasize the fact that the most important knowledge which the surgeon required today in his cancer work was the result of an accurate and impartial investigation into the efficacy of different methods of treatment. He was anxious for more information about the living pathology of the condition. He was also anxious that his friend, colleague and helper, the radiotherapist, should be assisted to develop his technique and to review his results, so that surgeons would know when to advise this method of treatment with the confidence that it was in the best interests of the patient to do so. The surgeon was equally concerned that assistance should be given to pathologists to correlate their findings with the clinical history of each patient. Like everybody else, the surgeon was anxious that the cause of the disease should be discovered and felt that assistance in this work should be given when it was possible that good would come. At the same time he hoped that the Anti-Cancer Council would devote its time and its money to an attempt to improve the treatment of this disease in this State, in preference to dissipating a large proportion of it in chasing a chimera of research work.

DR. FRANK STEPHENS, in stating the position from the radiotherapeutic aspect, said that all would agree that radiotherapy was of great value in the treatment of cancer. By present methods of radiation many cancerous and precancerous growths were completely arrested, and in less favourable cases one might almost always expect amelioration of symptoms with increased comfort and prolongation of life.

Though much was known about cancer and its treatment, it was to be hoped that in the near future further facilities would be made available, in order that full use might be made of this knowledge. The interests of the cancer patient demanded that all effective measures should be made available to him immediately the condition was diagnosed. Such measures included: (i) close cooperation of surgeon, pathologist and radiologist; (ii) an adequate supply of radium; (iii) modern X ray therapy apparatus; (iv) suitable hospital accommodation, which included after-care for patients with advanced growths, who were unsuitable for further irradiation.

The cancer patient attending a public hospital should be treated as an urgent case and should not be kept waiting for weeks before treatment was commenced, as was too often the case.

Considering that new methods took years to prove, progress in radiotherapy had been rapid and substantial. Progress had been possible mainly because apparatus for X ray therapy had improved, radium was available in large amounts, dosage could be accurately measured, both on the skin and at every depth-level in the body. And, most important of all, knowledge of the nature of the cancer cell, its grades of malignancy and its radiosensitivity, had increased with experience.

Turning to the mode of action of radiation, Dr. Stephens said that although the effect of irradiation was not fully understood, some ways in which it acted were known. These were: first, by destruction of cancer cells; secondly, by modification of the growth of undestroyed cells; thirdly, by reaction of the surrounding tissue; fourthly, by diminution of the blood supply.

The main effect of irradiation on the tissues might be varied by the type used and the method of application. In large intensive dosage irradiation produced chiefly a caustic effect, which, however, had the advantage over other destructive agents in that it also produced, by its selective action, sterilization over a wide area of tissue. This effect was most useful in the treatment of localized surface tumours and might be produced by radium or contact therapy.

The last-mentioned method provided one of the latest advances in radiotherapy and would be referred to more fully later on. The other effect, largely depending for its success on the selective action of radiation, was achieved by the radium bomb and highly filtered deep X rays. These agents were mostly used in the treatment of deep-seated inaccessible tumours.

Both methods were of value in their own spheres. Dr. Stephens said that he wished to point out here that there were few subjects on which medical opinions differed so consistently as upon the relative values of the various methods of irradiation. This was borne out by the fact that at the present day there were two main schools of experiment. One was experimenting with low voltages, the other with high voltages, and both would probably obtain improved results, but in different types of growth.

Radiotherapy, like surgery, was a purely local method of treatment, so that the types of growth which gave the largest percentage of cures were those that were regionally malignant, and those that metastasized to distant organs only late in their development.

In the following tumours the use of X rays or radium was usually the method of choice: precancerous conditions, such as keratoses and papillomata, and epithelioma of the skin. Radiation usually produced complete cure, leaving only a faint scar.

Response was not so good when cartilage or bone was involved or in cases in which relapse had occurred after inadequate radiation treatment. It was usual to treat the lymph drainage areas in the ulcerating variety by prophylactic irradiation, though this seemed unnecessary in proliferative growths.

In cancer of the buccal cavity, lip, tongue, tonsil, floor of the mouth, larynx and nasal accessory sinuses, radiation was often the method of choice for the primary lesion; also in parotid tumours and tumours of the cervix. When, however, glands were involved and operable block dissection, followed by irradiation, gave the best results, and whether glands were obviously involved or not, in

carcinoma of the tongue block dissection of the cervical regions on both sides was advised.

Cancer of the breast presented a different problem, and should be treated only after consultation with a surgeon. Generally speaking, Dr. Stephens thought that patients with operable conditions should be treated surgically and by irradiation. Irradiation might be pre-operative, at the time of operation, or post-operative; it might be a combination of all three, according to the site and type of growth.

There was one type of operable cancer of the breast, however, in which radiation results were better than those of combined surgery and radiotherapy. This was the scirrhous cancer occurring in women of about fifty years; surgery sometimes aggravated this condition, but many apparent cures were obtained by radiotherapy.

Many excellent results were obtained by radiation of inoperable cancer of the breast, indicating that, with further improvement in methods, this might become in the near future the method of choice in all stages of this disease.

The palliative effect to be expected in the treatment of metastases from breast cancer depended on the organ involved. Skin secondaries were easily controlled. The pain from bone metastases was relieved and secondaries in the mediastinum and upper lung fields had been controlled for as long as three years. No attempt, however, should be made to irradiate secondary deposits in the liver or at the bases of the lungs.

What had been said of breast cancer might be applied to a varying degree in the treatment of cancer elsewhere. The results, however, depended on the situation, type and stage of the tumour. Generally speaking, the radio-sensitivity of a tumour varied with the radio-sensitivity of the tissue from which the tumour arose.

Certain findings were common to all tumours which were radio-sensitive to some degree, but which were not as a rule cured. In such there was usually distinct improvement after one month of treatment. This was manifested by reduction in the size of the tumour and improvement in the general condition of the patient. Pain was relieved, and, although the primary tumour might in time completely disappear, metastases usually occurred sooner or later, and caused death. Recurrent tumours responded less and less favourably.

Dr. Stephens then discussed accompanying and subsequent effects. He said that with intensive treatment of the abdomen radiation sickness frequently followed. This, however, could now be minimized by intramuscular injections of liver extract during the treatment, and by the use of suppositories of "Nembutal" at the time of treatment. Diarrhœa and frequency of micturition might follow intensive irradiation of the lower part of the abdomen. The former was alleviated by small daily doses of liquid paraffin. If hair-covered skin was irradiated, permanent epilation followed. The main contraindications to radiotherapy were marked cachexia, marked anæmia and refractory distant metastases.

In general terms the selection of treatment in cancer by radiation might be considered under one of the following groups:

1. Operable cancer:
   (*a*) Pre-operative radiation in some cases was of value in preparing the field for the surgeon, either by localizing the growth or, in the case of some brain tumours, by rendering the surrounding tissue less vascular.
   (*b*) Post-operative irradiation should be given in practically all cases of cancer.
2. Readily accessible operable or inoperable cancer:
   (*a*) Radium alone might be used.
   (*b*) X rays alone might be used.
   (*c*) A combination of radium and X rays might be used.
3. Inaccessible growths might be treated by high voltage X rays or by a radium bomb.

Patients suffering from syphilis, diabetes *et cetera* should have appropriate treatment before irradiation was commenced.

Radiotherapy was often a help in differential diagnosis. This was seen in abdominal tumours, when a short preliminary dose of deep therapy would often help to decide between an inflammatory and malignant mass. For instance, pericolic inflammatory collections associated with diverticula melted away under irradiation, whereas neoplasms were unaffected.

Adenopathies of doubtful nature in certain cases should be irradiated before biopsy, to exclude the risk of dissemination.

As a general rule, the primary tumour was more radio-sensitive than secondary deposits. This was, however, not always the case; peritoneal sowings had been proved by subsequent operation to be more sensitive than ovarian tumours from which they had arisen.

The effect of irradiation on sarcoma was similar to that on carcinoma, except that distant metastases were as a rule more radio-sensitive.

Discussing low voltage X ray therapy, Dr. Stephens said that during recent years some amazing results had been obtained by the treatment of malignant tumours by concentrated, fractionated, short-distance irradiation or so-called "contact therapy". The method had been developed by Professor Chauol, of Berlin, and arose from the appreciation of the fact that the apparent superiority of radium to Röntgen therapy was not founded on the quality of the rays, but solely on the method of application.

The theoretical justifications for the treatment were as follows:

1. The clinical effect of the same dose of X rays of different wave-lengths was the same, the important factors being the energy absorbed and the time spacing of irradiations.
2. To expedite subsequent healing, the surrounding healthy tissues should be spared irradiation as far as possible.
3. The distribution of irradiation in the tissues was similar to that obtained with radium surface applicators and bombs. Contact therapy, however, owing to the high dosage rates available, provided for much shorter treatments, and confinement to hospital was unnecessary. The difference due to dosage rate was apparently of little importance, providing the fractionation of the radiation was maintained.

Treatment was carried out in daily doses, and the total dose depended on the reaction of the lesion to treatment. Regression of the lesion was occasionally noted by the third day. The skin reaction was similar to that following radium, but appeared more rapidly. With intense irradiation skin sloughing resulted, but epithelialization rapidly proceeded from the periphery. The patient was free from constitutional after-effects owing to the localized action of the beam.

The indications for low voltage X ray therapy were as follow: skin cancer, such as rodent ulcer and epitheliomata; melanomata, carcinoma of the lip, carcinoma of the tongue and tonsil, buccal mucous membrane and floor of the mouth, parotid tumours, thyreoid and mammary carcinoma.

The extension of the method to other sites, such as stomach, œsophagus, larynx or prostate, might be attempted, provided satisfactory surgery of access was developed and tumours were rendered directly accessible to irradiation. Benign lesions reacted in the same way as they did to radium.

Contact therapy undoubtedly had many advantages in its own field, which as yet was scarcely defined. How the ultimate results of this technique would compare with those commonly in use, it was impossible to say, but this method would probably prove a substitute for radium therapy in many forms of cancer.

Professor Chauol had within the last few months reported results obtained by him in the treatment of nine cases of rectal carcinoma by contact therapy after surgery of access. His results were as follows. Of the nine patients treated in this way, eight had suffered from severe and inoperable conditions, the ninth was considered to have a border-line operable tumour. Six out of the nine had shown complete disappearance of the tumour, the condition of the first patient treated having remained

arrested for two years. Of the two patients who were unsuccessfully treated, one had had after operation a recurrence which failed to react to further contact therapy.

In his concluding remarks Dr. Stephens said that, in spite of the fact that the results were limited to a small number of patients and a restricted observation time, they gained in importance because they had been obtained in a consecutive series of patients who were affected with severe carcinoma and who were unsuitable for any other kind of treatment. Operative measures were entirely out of the question. On the other hand, deep therapy treatment yielded no definite successes in these cases. Similarly, the prospects of success with the interstitial use of radium were limited to operable cases. In view of these facts, the suggestion that contact therapy should also be tried in cases of operable *carcinoma recti* seemed justified. In the meantime it might be expected that by a successful development of this new method, which was based on cooperation of surgical and radiotherapeutic procedures, the total number of carcinomata which could be successfully treated would be considerably increased.

DR. M. J. HOLMES, of the Commonwealth Department of Health, said that the subject on which he had been invited to speak was national organization against cancer in Australia. But before he endeavoured to explain in what the national organization consisted, he wished to take the opportunity of expressing to the Council of the Victorian Branch of the British Medical Association his deep appreciation of the honour done to him in inviting him to address the Branch on this subject, which was one in which he was deeply interested. He would also like to take the opportunity of assuring the Branch of the sincere desire of the department to which he belonged, to cooperate with the British Medical Association in handling the problems of this and other diseases.

Now that special efforts were being made in organization for combating cancer, one was met by the comment: "Why all this organization against cancer, a disease which kills late in life, when tuberculosis, which causes so much of its mortality in early life, remains so great a scourge?" To that Dr. Holmes replied: "Let us by all means devote all the time, energy and money we can muster to the control of tuberculosis. This is a disease about which we know much more than about cancer—a disease that we could, if we would, control to such an extent that it would practically cease to exist among us, as many another disease has in the past been controlled and wiped out."

Money and energy and effort spent on tuberculosis would be wisely and profitably spent, and much more should be spent. It could justify its expenditure a hundredfold. But it did not follow that cancer should not be effectively combated or that they should wait until the incidence of tuberculosis had diminished. Also the contention that cancer killed late in life was only partly true. Sarcoma attacked and killed at all ages, and one woman in every four who died in middle age, died of carcinoma. As a matter of fact, in 1933 in Australia 215 women in middle age, 40 to 55 years, died of tuberculosis; but 811 women died of cancer in the same age period.

No one knowing the cancer situation today could believe that it was not necessary to spend all the energy and money that could be mustered to control it and to lessen its toll in life, pain, sorrow and distress. To spend this money and effort wisely, suitable organization was necessary.

It would be asked: "What is this national organization?" "How is it constituted?" "What does it do?" "What has it accomplished?" Dr. Holmes would endeavour to answer these questions. He did not propose, however, to go into great detail in respect of the various activities which constituted the national organization for the control of cancer in Australia, but would indicate briefly the more important features of this organization and something of what had been accomplished by it.

The national organization to combat cancer in Australia was designedly loose, but it nevertheless functioned actively, continuously and successfully. It was made up of a number of units. These included not only the several State organizations specially constituted for combating cancer, but also various bodies and institutions associated with the actual treatment of cancer and with research into malignant disease. The necessary coordinating factor between all these independent units was provided, not in the form of a body specially constituted for the purpose and working through a committee, but as an activity based upon the Commonwealth Department of Health, which performed its coordinating work largely through the medium of an annual meeting of representatives of all the units concerned. This annual meeting was known as the Australian Cancer Conference.

The State organizations specially constituted to undertake cancer control work within the several States were the following: in New South Wales, the Sydney University Cancer Research Committee; in Queensland, the Queensland Cancer Trust; in South Australia, the South Australian Anti-Cancer Campaign Committee; in Western Australia, the Perth Hospital Cancer Trust; in Tasmania, the Tasmanian Cancer Committee; and in Victoria, the recently formed Anti-Cancer Council. It was hoped that the last-mentioned organization would work in complete cooperation with the similar agencies in the other Australian States and with the Commonwealth Department of Health, and would take its full share in the national organization.

In addition to these specially constituted State organizations, there were a number of other bodies which were closely associated with the work of cancer investigation and control, and which participated actively in the annual cancer conference. These bodies were the State Departments of Health, the several State universities, the research institutions, the British Medical Association, the Royal Australasian College of Surgeons, the Australian and New Zealand Association of Radiology, and the principal hospitals having radiotherapeutic departments or making special provision for the treatment of cancer by other means. The work of all these various organizations and institutions, although independent, was yet coordinated with a sufficient degree of practical interrelationship and mutual assistance to constitute an active and successful national organization. In this national organization, as already stated, the Commonwealth Department of Health acted as the coordinating factor. The Commonwealth Department of Health convened the annual cancer conference, followed up the various resolutions of the conference, maintained continuity of concerted action between conferences, and undertook certain work of a nation-wide character outside the bounds of the activities which were a function of the individual States.

The advantages of combating cancer from a broad national point of view were obvious. By providing for coordination between the several independent States, a uniform policy on the main issues could be defined and worked to; and by the pooling of the experience of the States the lines of progressive development could be determined from time to time much more satisfactorily than would be the case if every State were to carry on independently and without reference to the difficulties experienced or the progress made in the other States. The national organization did not interfere in any way with independent administration of control measures within States, but it coordinated efforts along the lines of a broad national scheme.

Dr. Holmes then indicated some of the directions in which the determination of uniform policy on main issues had been accomplished, and in which progress had been made as the result of the periodical meeting together of representatives of all the units, and the pooling of the experience gained by the individual units. He began with the first step taken in the formation of the present national organization.

He said that in the state of knowledge regarding cancer which existed some ten years ago, and which still existed, any scheme for the control of the disease would of necessity rest primarily upon the development of the most complete and modern facilities for examination, diagnosis and treatment, so that cases might be recognized as early as possible in the course of the disease and so that the proper method of treatment might be selected and applied without delay. This did not, of course,

mean that preventive measures should not be applied to the fullest extent that present knowledge permitted; but, until much more was known than was known at present, they could not plan a campaign based on preventive measures, and it was necessary to rely mainly on the weapons of early diagnosis and early application of properly selected treatment. This rendered necessary the formation and maintenance of properly equipped and staffed modern cancer clinics.

This fact had been fully recognized by the Commonwealth Department of Health when, ten years previously, it had strongly supported the suggestion of Colonel Cameron, Member for Brisbane in the House of Representatives, that the Commonwealth Government should purchase a supply of radium for use in Australia, so that this modern remedy might be available to Australian citizens who could not afford the expense of going abroad for treatment. In 1927 ten grammes of radium had been purchased by the Commonwealth Government at the instance of the Minister for Health, Sir Neville Howse, V.C., at a cost of £100,000. The greater part of this radium had been issued on loan, free of cost, to certain large hospitals, which agreed to build, equip and maintain efficient clinics, with a sufficiently experienced staff to utilize the radium to the best advantage and to develop other methods of treatment. In this way the special clinics had been established in the several States. The Commonwealth Government had also agreed to make a grant of money to those States which set up an organization for the control of cancer and for the collection of funds for this purpose. In two States an organization of this character had been established in the same year (1927). In New South Wales the Cancer Research Committee of the University of Sydney, and in Queensland the Queensland Cancer Campaign Committee, had commenced operations during 1927. In 1929 the work of the Queensland Cancer Campaign Committee had been taken over by the Queensland Cancer Trust.

In 1928 South Australia had formed a General Committee for Cancer Treatment and Research, and in the same year the Perth Hospital Cancer Trust had been established. In 1932 the Northern Tasmanian Anti-Cancer Campaign Committee had come into being, followed by the Southern Tasmanian Anti-Cancer Campaign Committee in 1934. These two bodies in 1935 had selected representatives to form the Tasmanian Cancer Committee. In Victoria the Anti-Cancer Council had been established in 1936 and was, as those present knew, preparing for an appeal for funds. To each of these State organizations the Commonwealth Government had granted £5,000, which was supplemented by a similar amount from State Governments, and which was also supplemented by public subscriptions. In this way the State organizations, which were independent units in the national organization, had been formed in each State.

Within a year, by 1929, cancer clinics had been set up with well-equipped accommodation in eleven large hospitals in the capital cities of Australia, with two or three subsidiary clinics in extra-metropolitan centres. The number of special clinics had now increased to eighteen in the metropolitan areas and eight in extra-metropolitan centres.

When the Commonwealth Government issued radium on loan, free of charge, to those clinics which had been specially equipped for the purpose, it had imposed certain conditions, designed to promote efficiency and uniformity in the main principles of its employment, and each institution concerned had entered into an agreement with the Commonwealth Department of Health accordingly, which agreement still stood. Among these conditions was one relating to the promotion of research by the collection of necessary data and the carrying out of adequate pathological examinations *et cetera*, and one relating to the keeping of case records on uniform lines, the full recording of treatment and its results, and the following up of the patient after treatment and after leaving the clinic, so that the end results of the treatment might be accurately recorded. This had laid the foundation of a uniform system of records throughout Australia.

When the Commonwealth Government purchased the radium and issued it to suitably equipped and staffed clinics, it had recognized that radiotherapy was in its infancy; that experience would lead to variations in technique; that it would be necessary from time to time to vary the way in which the radium was mounted. It had also recognized that little was known of the real dangers of radium and that measures of protection both for patients and staff would have to be investigated and applied. It had realized also that readjustments would have to be made in the distribution of the radium among the various hospitals, in order that the most efficient use should be made of it. The Commonwealth Department of Health had therefore set up a Radium Laboratory in conjunction with the University of Melbourne, to investigate the physical problems of radium and to make the results of its investigations available to all radium treatment centres. This laboratory also carried out the work of altering the mounting and screenage of containers, as experience dictated.

The variation in the mounting of fixed radium containers was a slow and costly process, and so, bearing in mind that experience would necessitate such costly alterations in mounting of fixed radium containers, the Commonwealth Department of Health had decided that a proportion of the radium should be held as soluble radium salt and used for the preparation of radon. This radon could be mounted in any way that experience might indicate to be desirable. The Commonwealth Radium Laboratory had set itself to investigate the problems of mounting and issuing radon and to develop a technique which was now standardized for all Australia. Radon was made available mounted in flexible needles of any length, strength and screenage desired for any particular operation. The result of this work was that in Melbourne there was one of the largest radon-producing centres in the world, and Melbourne might claim that nowhere else in the world had radon treatment techniques reached a higher standard of efficiency or a higher range of success. Radon centres had been developed also at the Universities of Sydney, Adelaide and Western Australia, and the setting up of a radon centre was now actively proceeding at Brisbane, in the University of Queensland. In all these centres the radon was prepared from Commonwealth radium, and the technique was standardized. The standardization would have been impossible without national organization. There was, then, an efficient radon service throughout Australia.

The experience gained so far in the physical aspects of radium and radon therapy had been summarized in a handbook prepared by the Commonwealth X-Ray and Radium Laboratory; the Commonwealth Department of Health was about to publish this handbook and to issue it free to all to whom it might be of interest and value.

Arrangements had been made also for the publication of the work of the laboratory in relation to the investigation of the physical problems of X ray therapy, so that the information might be immediately available to physicists and to radiologists using this method of treatment. A preliminary article had been published in THE MEDICAL JOURNAL OF AUSTRALIA of January 16, 1937.

The problems of radium and radon therapy having been successfully dealt with in this way, the Australian Cancer Conference had asked the Commonwealth Department of Health to extend the scope of the Commonwealth Radium Laboratory to undertake investigation of the difficult physical problems of X ray therapy, and to set up the necessary standards for the measurement of X ray dosage and for the determination of the quality of X ray output from the various plants employed in radiation therapy. It had asked also that the development of local physical services in the several States should be facilitated and that the Commonwealth should appoint a competent physicist to visit the several States in a consultative capacity. This had been done at once, and in conjunction with the Council of the University of Melbourne, the Commonwealth Radium Laboratory in 1935 had been reorganized to undertake the wider scope of work. This laboratory was now designated the Commonwealth X-Ray and Radium Laboratory, and the physicist-in-charge was made available to visit all States, as required by the

States, in order to encourage and to facilitate the establishment of the physical services in each State, so necessary to the accurate administration of radium and X rays in treatment.

The Commonwealth X-Ray and Radium Laboratory had set up at its laboratory at the University of Melbourne a primary standard of X ray dosage against which all X ray dosage measuring instruments in Australia could be calibrated. The calibration was done by calibrating a portable standard against the primary standard free air chamber over a wide range of qualities and conveying the portable standard to institutions or elsewhere where the X ray dosimeters required to be calibrated. Substandards were being set up in the several States, which could also be calibrated against the primary standard. A standard of kilovoltage had also been set up at the laboratory.

Problems in radiological physics were being investigated at the laboratory, and for this purpose data were being collected from the radiotherapeutic departments of the hospitals throughout Australia. In every State except Victoria a local physical service had been set up, based on the State university, and the physics departments of all these universities were cooperating actively with the Commonwealth X-Ray and Radium Laboratory at the University of Melbourne. During the previous year, three States—South Australia, Queensland and Tasmania—had appointed specially qualified physicists to work in conjunction with the radiotherapeutic departments of the hospitals. New South Wales had had such a physicist for some time, and in Western Australia there was close cooperation between the Physics Department of the University of Western Australia and the Perth Hospital Radiotherapeutic Department. In Victoria there was as yet no local physical service, but the Commonwealth X-Ray and Radium Laboratory and the Physics Department of the University of Melbourne had been working closely with the radiotherapeutic departments of the hospitals and had given necessary advice. It was hoped, however, that with the establishment of the Victorian Anti-Cancer Council a local physical service would be shortly developed, based on the Physics Department of the University of Melbourne.

It would be noted, therefore, that, starting from an issue of radium by the Commonwealth Government for treatment purposes to hospitals throughout Australia, there had grown up: (*a*) A system of State organizations for control of cancer. (*b*) A large number of specially equipped and staffed clinics, which were operating very actively throughout Australia. (*c*) A high degree of uniformity and standardization throughout Australia in respect of techniques and of case-recording, and in the compilation of statistical material regarding treatment and its end results. (*d*) The development of a system for the use of radon in treatment throughout Australia and the standardization of the issue and use of the radon. (*e*) The setting up of a primary standard for the measurement of X ray dosage and for the measurement of voltages, and arrangements throughout Australia for the calibration of measuring instruments against the primary standards. (*f*) Physical services in all the States of Australia employed in collecting necessary data and in investigating the problems and difficulties of the radiotherapists, pooling their experience, and working actively with a central laboratory, the Commonwealth X-Ray and Radium Laboratory, which had the fullest cooperation with the physics departments of all the universities in Australia and with the radiotherapeutic departments of all hospitals. This meant that X ray and radium treatment all over Australia had been put on an accurate scientific basis with accurately measured dosage.

This, then, was one phase of the activities of the national organization for control of cancer in Australia. The whole of the work was closely coordinated by the Commonwealth Department of Health, and the units in the scheme met anually in conference to discuss progress and to advise upon future developments.

Dr. Holmes then discussed protection and health hazards in the use of radium and X rays. He said that the use of radiation methods of treatment was associated with considerable risk both to operator and patient, unless appropriate precautions were taken. These precautions had been enunciated in certain international recommendations for X ray and radium protection. Through the agency of the Australian Cancer Conference and the Commonwealth X-Ray and Radium Laboratory, these international recommendations had been adopted in all Australian institutions and had been carefully carried out. Protection to workers had been provided by various devices, including the placing of a suitable thickness of lead between workers and the source of radiation, and considerable amounts of money had been expended by the various institutions in ensuring adequate protection to their staffs. Not only had this been done, but concerted action had been taken throughout Australia to measure the actual amount of radiation to which workers in the various establishments were being exposed, and to determine whether such radiation was within what was known as a tolerance dose. Careful periodical blood examinations of all workers were also made. Departures from normal health in radium and X ray workers were investigated by a Health Hazards Committee established in association with the Commonwealth X-Ray and Radium Laboratory.

The principles of protection from radiation had been summarized by the Commonwealth Radium Laboratory in a booklet published by the Commonwealth Department of Health and issued without cost to all institutions and to all radiologists for their information and guidance. It might then be claimed that this important question of "protection" was receiving unremitting attention at all institutions where radium and X rays were being used in Australia. Its problems still continued to be investigated by the Commonwealth X-Ray and Radium Laboratory, and data were being regularly gathered from the radiotherapeutic departments of hospitals and from other institutions using radium and X rays.

Turning to the question of research, Dr. Holmes said that the national organization had not so far taken any active part in relation to research work in Australia directed towards the determination of the causes of cancer. This work was of an exceedingly complicated character, requiring the closest interrelationship between biophysicists, biochemists, pathologists and other research workers in any specially equipped laboratories. Individual work on isolated problems was not of much value in this respect. In Australia there were not the same opportunities for adequate research into the causation of cancer as were enjoyed in some other countries, where large and well-endowed research laboratories were working in close cooperation with one another. It had seemed that workers in Australia should rather concentrate their limited resources on fields of statistical, clinical and physical research in which they could do really useful work. Dr. Holmes said that he had already indicated the work that was going on throughout Australia, in the Commonwealth X-Ray and Radium Laboratories, and in the departments of physics of Australian universities and in the radiotherapeutic departments of hospitals in relation to the difficult physical problems of radiation therapy. This work was thoroughly well coordinated under the national organization and was being carried out successfully and with the greatest practical benefit to the radiologists who were applying radiation in the treatment of human diseases.

The recently formed National Health and Medical Research Council, at its first meeting, held in Hobart in February, 1937, had considered the question of medical research in Australia from various aspects. It had emphasized the great need for clinical research in relation to a number of diseases, and the great value obtainable from such research if properly pursued. Clinical research adequately carried out would provide a key to success in the control and treatment of many diseases of which at present knowledge was very limited. The council had pointed out that clinical research was fundamentally dependent upon the keeping of efficient records of the patients suffering from the disease which was being investigated. It had deplored the fact that the case records available at hospitals throughout Australia were almost valueless and that consequently the clinical research worker had no reliable data on which to work. In his

presidential address to the British Empire Cancer Campaign in 1933 the chairman had said:

> Careful recording of all cases of cancer that have been treated, including the following up of such cases to ascertain their subsequent history, is considered a very important branch of research, as such records tell us which methods are the most successful and which are unsatisfactory.

The necessity for keeping adequate records had been recognized early by the Commonwealth Department of Health, and a considerable degree of success had been obtained by the national organization in this direction.

As Dr. Holmes had already stated, one of the conditions under which the Commonwealth Department of Health made radium available to the specially equipped hospitals was "the keeping on uniform lines of records of the cases treated at the clinics, and of the results of treatment", and "the compilation of statistics of results obtained by various methods of treatment, and to this end the establishment of an efficient system for following the patients up after treatment and after leaving the clinic in order to ascertain the end results".

The clinics were the real basis of the campaign against cancer in its present stage of development. Under the scheme of national organization in Australia the system under which clinics were formed at the principal hospitals throughout Australia provided for the uniform recording of details regarding all patients treated; for detailed recording of actual treatment given; for following the patient up after treatment, and after he left the clinic until the end result of the treatment (cure or death) had been ascertained; for laboratory diagnosis and for laboratory control of treatment. It provided also for the selection of the most appropriate form of treatment for each individual patient. This selection of treatment in most clinics was made by a consultative group of surgeons, radiologists, gynæcologists, pathologists, dermatologists, who met in consultation to see all new patients attending the clinic and to study the results obtained.

In order that case records might be uniformly kept, the Commonwealth Department of Health, with the assistance of a committee appointed by the Australian Cancer Conference, had drawn up a form of case sheet. These sheets were printed by the Commonwealth Department of Health and distributed free to all the clinics. Several thousands were used every year.

The system for following up patients after they left the clinic on completion of treatment had not been attended with equal success at all the clinics. At first the system had been applied only to patients treated with radium; later it was extended to cover all patients subjected to any method of radiation treatment, and finally to patients treated surgically or by any other method. In some of the largest hospitals the records now went back some ten years, and the percentage of patients of whom trace had been lost was very small (less than 6%). In other words, of the total patients treated by the clinic in the previous ten years, it was possible, for example, to indicate in 94% of the cases the survival rate; and in respect of those who had died, the length of time elapsing between treatment and death. Full details of the patient's history and progress were kept.

As already stated, not all the special clinics had developed so efficient a records and follow-up system. In a few of the clinics the records were still very incomplete and the follow-up system almost non-existent, but the number of such clinics became fewer each year.

The use of the uniform case sheets throughout Australia made possible the compilation of statistical data covering the whole of Australia. As records were kept on uniform lines, data could be extracted in such a way as to be capable of consolidation for all Australia. For example, if it was desired to collect data regarding the results of various methods of treatment of any particular type of cancer, this could be done without difficulty, the information being collected from the various clinics and consolidated into one comprehensive tabulation. At the present time records were available of more than 25,000 patients treated by means of radium or radium combined with other methods, and in addition records of a very large number of patients in whose treatment radium had not been employed.

Next month the eighth Australian Cancer Conference would be held at Canberra. For this conference a compilation was being made covering cancer of the skin and of the lip. Within the space of a few weeks it had been possible to obtain from those clinics which had developed efficient systems of recording cases and of following up patients after treatment, data regarding 10,000 patients suffering from skin and lip cancer and who had received their treatment three years or more ago. The data collected enabled separate tabulations to be made of the results of eighteen different methods of treatment. Separate tabulations were also made for patients treated ten years, nine years and eight years previously, and so on. Separate tabulations had been made in respect of the different pathological types of the disease; for example, basal-celled carcinoma (rodent ulcer) was tabulated separately from squamous epithelioma and from the transitional types of carcinoma. Melanoma was separately dealt with, as also were the hyperkeratoses. The results of treatment were also tabulated in respect of five different stages in the disease, from the earliest stage to the most advanced. The tabulations also covered age distribution of cases, sex distribution, geographical distribution, race distribution, occupation, and so on. The compilation of this material available from the case records of some 10,000 cases necessitated the preparation by the Commonwealth Department of Health of some scores of consolidated tabulations; and Dr. Holmes stated again that this material was prepared and consolidated within the space of a few weeks.

It was not claimed that the data in respect of all these desiderata were complete, but Dr. Holmes thought that it could be safely claimed that in respect of no other disease would it be possible to obtain from hospitals all over Australia within a few weeks of request such a wide range of data for so large a number of patients, and in a form permitting of ready consolidation into statistical tables for the whole Commonwealth. This had been made possible by the persistent stimulation of the clinics by the Commonwealth Department of Health and by the Australian Cancer Conference, and by the annual request for compilation of data which the Commonwealth Department of Health was able to make by reason of the conditions of its agreement with the various hospitals holding Commonwealth radium. The hospitals concerned were, however, handicapped by shortage of staff for records and follow-up work. If money were made available for employment of a suitable staff, the value of the records would be very greatly increased, and it was considered to be a most important duty of the anti-cancer organization in each State to foster the building up of an efficient records and follow-up system in each of the hospitals. The proper investigation of any disease was dependent primarily upon accurate data obtained through an efficient records and follow-up system.

The success already attained in respect of the investigation of cancer under the national organization was encouraging, but was very much short of what could be done in this field.

Statistical research was not confined to the field of case records and results of treatment. The Commonwealth Department of Health made an annual survey of mortality statistics, following upon a comprehensive review of cancer mortality in Australia, which Dr. Holmes had compiled in 1925. It had been found, for example, that mortality from cancer in age groups under sixty-five years was falling in Australia and that the rise in mortality in age groups over sixty-five years depended to a large extent upon the ageing of the population and to the transfer of death certifications from the category of senility to the more exact categories of cancer and certain other diseases. Those present would remember that Dr. Cumpston, the Director-General of Health, had drawn attention to these factors in his opening address to the last Australian Cancer Conference, on the trend of cancer mortality. (This had been published in the *British Journal of Hygiene*.)

One other direction in which the national organization against cancer in Australia was moving in relation to the investigation of the disease was the effort to obtain more accurate information regarding the incidence of pathological types of cancer in Australia and of the mortality from these types. Information in this respect could not be gathered from death certificates because most general practitioners were usually not in a position to give accurate information regarding the pathological type of the disease causing death in any given case. An attempt was to be made to induce hospitals with properly equipped pathological departments to record on cards particulars regarding pathological types of cancer in persons entering the hospital. Compilation would then be made from these cards by the Commonwealth Department of Health. For this purpose it would be necessary to devise a scheme of pathological classification of cancer on which the hospitals could work, because obviously all the hospitals should follow the same scheme of classification; otherwise a consolidated compilation could not be made. As reliable conclusions could be drawn only from sufficiently large masses of figures, consolidation was essential.

It would be noted then that in the field of clinical research the national organization had already accomplished a good deal and was widening the field in which accurate data were being collected.

There were other fields in which the national organization was operating, but time was passing. Dr. Holmes wished, however, to refer briefly to the international relationships which were maintained with other countries interested in the control of cancer. The Commonwealth Department of Health, in its official relationships with other countries through the Health Organization of the League of Nations and otherwise, regularly obtained information regarding developments in these countries. It also transmitted to other countries information regarding developments in Australia. Prominent workers in the cancer field in Australia who went abroad to study developments overseas had been commissioned to make reports to the Commonwealth Government on their return, and these reports were printed by the Commonwealth Department of Health for the information of the Australian Cancer Conference; these reports were discussed at the conferences. Australia also cooperated in certain international investigations in the field of cancer, notably in the investigation into the results of the use of radium in the treatment of cancer of the uterus.

In the field of public education the national organization itself had not yet played any very appreciable part. At the request of the Australian Cancer Conference the Commonwealth Department of Health had in 1932 undertaken an educational campaign for some months through the Press and otherwise, and some 200,000 leaflets had been distributed to the homes of the people. But it had been considered that public education was, generally speaking, a matter for each State organization to handle in the way best suited to each State.

Dr. Holmes then referred to the part of the annual Australian Cancer Conference in the national organization. He said that when the Commonwealth Government purchased radium in 1927 it had formed a Cancer Advisory Committee to assist it in laying down conditions covering the distribution and use of the radium. When the cancer clinics had been established and the State organizations had been formed, it became apparent that provision had to be made for a larger conference offering possibilities for discussion and for determining lines of development. The Cancer Advisory Committee had therefore been discontinued and the Australian Cancer Conference was substituted for it in 1930. There had been a conference annually since that date, and the one to be held next month was the eighth of the series.

These conferences provided the real connecting link between the units forming the national organization. They were attended not only by representatives of the various State organizations for the control of cancer, the Australian universities and research centres, the Royal Australasian College of Surgeons, the State Branches of the British Medical Association, and the large treatment institutions throughout Australia, but also by individual surgeons, radiologists, pathologists, physicists and others working in the field of cancer investigation and treatment in Australia. New Zealand had also been well represented at many of the conferences. The range of subjects discussed at the conferences covered the whole field of effort against cancer in Australia and New Zealand, and also the matter of international cooperation.

These conferences had thus provided the means of bringing together for mutual beneficial discussion, research workers, surgeons, radiologists, physicists, pathologists, statisticians and administrative officers—lay and medical. They had been successful in bringing about a considerable degree of coordination and concerted action throughout Australia and had provided the opportunity of taking stock annually and of reviewing progress and results, and also for discussing problems and developments for reaching conclusions as to the lines to be followed in respect of future action. The direction of energy along selected channels, instead of its dispersion in uncoordinated directions, had been aimed at and had already to some extent been successfully achieved.

It would be difficult to exaggerate the value that these conferences had had in stimulating thought and in securing uniform progress in the campaign against cancer in Australia. The conferences had had far-reaching effects. The setting up of the Anti-Cancer Council in Victoria owed much to them; so also did the establishment of the recently formed National Health and Medical Research Council.

In Australia, where each State was an independent unit, the effective operation of cancer control measures had to depend upon the existence in each State of a strong State organization. Each State organization should be left to carry out its work within the State untrammelled. In these circumstances it was obviously not necessary to set up a separate national body to handle the details of control. This work was done in each State by each State. But organization had been necessary to provide for their mutual working together for the common good; for the pooling of experience, so that experience gained in any one State might be placed freely and rapidly at the disposal of the others; for the collection and consolidation of data; and for providing national services outside the scope of the work of the individual States.

After the annual conference the delegates dispersed. It was necessary to provide for converting into progressive action the conclusions and recommendations of the conference. The Commonwealth Department of Health had carried out all these necessary coordinating and executive functions within Australia. It also maintained the necessary international relationships with oversea countries. The national organization therefore was an association of independent units whose activities were coordinated by the Commonwealth Department of Health, with the essential assistance of an annual conference of representatives of all the units concerned.

Dr. Holmes concluded by saying that he had endeavoured to show how this national organization had grown up, how it worked, what it had accomplished. The organization was designedly loose, and it appeared to be suitable to the conditions existing in Australia. It functioned actively, harmoniously and successfully. Should the future show the need for more complete definition in the form of national organization for the control of cancer, no doubt the combined wisdom and experience of the representatives of the various units of the organization who met annually at the cancer conference to discuss this and all other matters relating to cancer in Australia, would indicate those directions in which improvement in the organization could be made.

DR. B. T. ZWAR said that the object of his remarks was to review briefly: (i) the history of the efforts made in Victoria to control cancer; (ii) the present movement to correlate and extend existing efforts; (iii) the part which might, and which it was hoped would, be played in this movement by members of the British Medical Association.

In Victoria the efforts which had preceded the present movement for controlled and collective action were similar to the sporadic actions in other parts of the Empire or,

for that matter, in the world at large. In England, for instance, a properly organized collective movement, instituted by the Ministry of Health in 1922 and by the British Cancer Campaign established in 1923, had been preceded by the formation of special cancer hospitals. There were the Cancer Hospital, established in 1851, the Christie Hospital of Manchester, established in 1892, and the Cancer Charity of Middlesex Hospital, now known as the Middlesex Cancer Hospital, tracing its origin to a bequest made as long ago as 1792. These hospitals, originally intended to provide institutional treatment for sufferers from cancer, regarded as incurable, had in the course of time widened their scope so as to provide treatment for all stages of the disease, as well as equipment for modern research. There were in addition the Imperial Cancer Research Fund, established in 1902, working under the direction of the Royal Colleges of Physicians and Surgeons; the Radium Institutes of London (1911) and Manchester (1915); and a Medical Research Council, which directed investigations and controlled considerable stocks of radium made available by the Government for therapeutic and research purposes.

In Victoria development of action had been on similar lines. The Austin Hospital for Incurables and Chronic Diseases, established in 1885, had from its inception provided special accommodation for sufferers from cancer in incurable stages of the disease. Dr. Zwar could still recall the harrowing and depressing sights which presented themselves in the cancer wards of that institution as long ago as during the first decade of this century. In those early years of this century it had not been infrequent to see patients in the cancer wards of the Austin Hospital with the greater portion of the soft and bony tissues of the face and anterior part of the base of the skull destroyed to such an extent as to leave the posterior wall of the pharynx and the base of the terrain exposed; and in these hapless patients it had been extremely difficult to prevent the infection of discharging ulcers by blowflies. In recalling these memories he appreciated the great advances which had been made since then, even in the treatment of cancer in its incurable stages.

As in the case of special cancer hospitals in England, advances in knowledge had led to a better equipment for treatment and to the establishment of a new cancer block at the Austin Hospital, where patients could receive the benefit of modern developments. This had been opened in 1931. There had been other, albeit sporadic, efforts to deal with the cancer problem in Victoria. In 1913 the late Sir John Grice (then Mr. John Grice) had founded a research scholarship in the University of Melbourne. The income from this scholarship supplemented from other sources had enabled Dr. Cherry and other workers to carry out research in the problems associated with the causation of cancer. Then there were the Cancer Research Committee of the University of Melbourne, the Walter and Eliza Hall Institute of Research in Pathology and Medicine, and the Baker Medical Research Institute, the research into physical problems associated with the treatment of cancer carried out by the Department of Physics in the University of Melbourne, the investigational work carried out by the Royal Australasian College of Surgeons. Finally, there were the special radiotherapeutic departments established at the Royal Melbourne, The Alfred, Saint Vincent's, Women's, Prince Henry's, and certain country hospitals. These institutions, in addition to their own privately owned radium, received on loan additional amounts from the Commonwealth Department of Health and were equipped with plants for deep and superficial X ray therapy and surgical diathermy units. All these institutions, however, had (particularly during the period of depression) found it extremely difficult and in fact impossible to keep up to date their equipment for the treatment of cancer patients.

All these activities in Victoria connected with the investigation and treatment of cancer had functioned independently and without coordination. This brought Dr. Zwar to the second part of his paper, namely, the present movement to correlate and extend existing efforts. It was embodied in the functions of the Anti-Cancer Council of Victoria, created in 1936 by a special Act of Parliament. The movement for its creation had been initiated by a former president of the Branch, Sir Stanley Argyle, when Premier of Victoria in 1934.

It had for its objects: (*a*) to coordinate in Victoria all activities in relation to research and investigations with respect to cancer and allied conditions and with respect to the causation, prevention and treatment thereof; (*b*) to promote and subsidize such research and investigations; (*c*) to provide maintenance and travelling expenses to persons in need who were suffering from cancer, to enable them to become inmates of or to attend a public general hospital or special cancer clinic for treatment; (*d*) to investigate the advisability of the establishment of special cancer clinics, and, if thought advisable, to establish such clinics; and (*e*) to facilitate the improvement of the treatment of persons suffering from cancer.

For carrying into effect these objects the council was empowered, subject to necessary safeguards, to obtain moneys by means of grants, subscriptions and gifts, to obtain and to hold property, to execute special trusts and to apply the capital and income of the funds and property for such purpose.

These powers of the Council were detailed in the Act as follows:

> (*a*) obtain moneys by means of grants subscriptions gifts bequests or otherwise and invest any moneys so obtained and hold investments of the same;
>
> (*b*) receive obtain and hold lands moneys securities and other property real or personal;
>
> (*c*) execute any special trusts in connexion with moneys or property received obtained and held by the council;
>
> (*d*) apply the capital and income of the funds and property of the council or any part thereof, subject to such trusts (if any), for or towards the foregoing objects; and
>
> (*e*) do all such things as are incidental or conducive to the attainment of the foregoing objects and the exercise of the powers of the council.

The affairs of the Anti-Cancer Council were administered by a council, an executive committee, a finance committee, a medical and scientific committee and an appeals committee. It was at present engaged in organizing an appeal and aimed at obtaining a sum of £100,000 in order to enable it to carry out the objects which had been outlined.

Lastly, Dr. Zwar discussed the part that it was desired members of the Branch should play in the movement.

At the outset it was the general and considered opinion that if the movement was to serve the community to the greatest advantage, it was important that it should receive the whole-hearted sympathy and cooperation of members of the medical profession and that the normal relationships which existed between members of the profession and their patients should in no way be disturbed by it. This had been the aim of the Council, and the appeals committee, in carrying out any necessary propaganda, had been guided by the principles laid down by the British Medical Association. Whilst the Council recognized the need for propaganda to carry out its objects, it appreciated the dangers of improperly controlled propaganda. It was fully alive to the importance of the experience in other countries. This had been specially referred to in a paper published in 1928 by Stanley P. Reimann and Frederick H. Safford, of Philadelphia, on a "Statistical Study of the Influence of the Educational Campaign on the Interval between Discovery and Consultation in Mammary Carcinoma". The authors, basing their finding on a fourteen years' educational campaign, concluded that: "There has been no inflection in the curve to indicate that the educational campaign begun in 1914 has had any effect." Their paper contained the following warning, which admirably expressed Dr. Zwar's considered opinion:

> If propaganda has failed to accelerate improvement, as the data clearly indicate, why has it failed? Inadequate time can hardly be a valid excuse. Fourteen years should be ample, although in the city

of Philadelphia it is only during the last three or four years that intensive effort has been made. Should the propaganda be increased until every newspaper every day carries some warning, until every radio set in every home every day enunciates at least once "be careful of cancer", until every week is cancer week? This is obviously a *reductio ad absurdum*. Popular cancer propaganda in the United States, and we suspect in other countries also, has some undesirable aspects. It has unduly disturbed the peace of mind of many normal individuals and made veritable "cancerophobes" of many. Other disadvantages will occur to the thoughtful physician which it is perhaps unprofitable to discuss in this paper. Some rearrangement of the methods seems desirable.

The same authors suggested that the general improvement which had taken place in dealing with cancer was in the main due to a better appreciation on the part of the physician of the advantages of early recognition and treatment. This raised the importance of early diagnosis and treatment, and the important part which had to be played by members of the medical profession with regard to it in any form of cancer campaign. To the audience present there was no need to lay stress on this, for it was universally recognized by members of the profession that cancer in its early stages was a local disease and with certain exceptions was curable by surgical measures locally applied. Unfortunately, however, it was true that the early stages of cancerous growths, whether they occurred in the breast, stomach, uterus or rectum, were so insidious and alarmed the unsuspecting patient so little that advice was not sought until manifest signs of the disease were present and the original local condition had become a generalized one and had passed from an easily curable condition to one that, in the present state of knowledge, was incurable. It was for the members of the medical profession to indicate the means for securing earlier diagnosis and treatment with a greater degree of regularity. The dangers of lay Press and other public forms of propaganda had been voiced already. The institution of medical examinations at regular intervals (of four or six months) for all persons approaching or in the cancer age might seem idealistic, but it was felt that if such periodic examinations became customary and were properly carried out, many cases of malignant disease would be diagnosed in an early and curable stage. There was no need for such a plan to disturb the existing relationship between patient, medical attendant and consultant; and it should receive the whole-hearted support and financial recognition of all life insurance organizations.

Whether such a plan of periodic examinations was adopted or not, medical students and practitioners should be instructed regarding the importance of and the best means for the early recognition and treatment of malignant disease. In Germany the campaign against cancer was under the direction of the German Central Committee for Cancer Control. It was one of the duties of that organization to provide for lectures to physicians and surgeons, informing them of the relative value of the methods of diagnosis and treatment of various forms of cancer as well as of any developments in those fields.

The cooperation of the profession was also required in establishing and carrying out proper systems of recording and following up of all cases of cancer, as had been stressed by other writers.

The final object of Dr. Zwar's paper was to plead with those present for some personal interest in the appeal about to be launched. If they were unable or disinclined to contribute themselves, their personal influence with those in a position to subscribe would be most helpful. It was the personal appeal that counted for more than anything else in such movements, and members of the profession were best able to make a personal and reasoned appeal.

DR. W. W. OSTERMEYER thanked those who had presented the subject so ably, and drew attention to the comparative neglect of the physiological aspect of the condition. He asked any physiologist present to contribute to the discussion. Dr. Ostermeyer referred to the possibility of making people psychologically cancer-minded to an excessive degree as the result of propaganda, and expressed the opinion that this might predispose such people to cancer for all that was known to the contrary.

DR. R. R. WETTENHALL said that dermatologists in Melbourne did not regard Professor Chauol's contact therapy as anything more than the introduction of a new means of applying knowledge as a result of the invention of a suitable applicator. Since 1906, when the late Dr. Herman Lawrence, of Melbourne, introduced the use of β rays of radium in treatment of surface lesions, the principle of shallow penetration with a small dose of radio-active substance had proved of great value; the very great proportion of rodent ulcers and pre-rodent skin lesions could be cleared up by means of one or two applications, and 90% of them remained clear. By means of the contact applicator of Professor Chauol and a ray of low penetration this principle could now be applied to regions hitherto inaccessible. Australia was very fortunate in the equipment now available at the University of Melbourne, where the work done compared favourably with that done anywhere else in the world. Dr. Wettenhall expressed a warning against the amount of exposure of the skin to sun and wind, which had become customary, and stated that dermatologists generally believed that such exposure was an important ætiological factor in the production of cancer of the skin. It was probable that in ten or twenty years the effects would be noticeable. Certain oculists had supported the dermatologists in this opinion. People whose skin peeled rather than became pigmented should particularly heed the warning. Dr. Wettenhall related the occurrence of keratosis in a patient at the age of twenty-one years, and mentioned a patient who had a rodent ulcer at eighteen years of age, which had proved rapidly fatal. He expressed the belief that cancerous conditions at an earlier age progressed more rapidly than those later in life.

DR. JOHN DALE asked for Australian statistics on the interval between discovery of the cancer by the subject and consultation with the doctor. He also referred to the necessity for careful attention to the wording of addresses intended to inform lay people about cancer, and thought that by this means it should be possible to avoid cancerphobia.

DR. J. NEWMAN MORRIS said that in an American report in 1932 the average period between discovery and consultation was stated to be seven months.

DR. IVAN MAXWELL, in reply to Dr. Ostermeyer, drew attention to the enormous amount of biochemical work, especially on sterols, which had been done in investigating such substances as factors in the causation of cancer. Substances containing the cholesterol ring were easily modified to produce cancerogenic substances that caused superficial cancers in experimental animals.

PROFESSOR MARSHALL ALLAN thanked those who had presented the subject so ably, and emphasized the need for the help of the profession, who could assist greatly in getting ready the sinews of war for the Anti-Cancer Council. Members could be assured that the Branch's representatives on the Anti-Cancer Council would see that the bad aspects especially of propaganda which had been noted elsewhere would be avoided in Victoria. Professor Allan thought that the use of the method of grading the malignancy coefficient of cells, which was being worked out in Moscow as an index of prognosis, might represent an advance and be used as a guide by the surgeon.

Dr. Holmes, in reply to Dr. Dale's question, pointed out that the interval between discovery and consultation varied with different types of cancer and with the location of the cancer; some nations had got figures out, but there were as yet no figures for Australia; patients' impressions and statements were unreliable. Special information about skin cancer for the meeting of the cancer conference to be held in April had been asked for. A compilation of the statistics on the stage at which patients reported with tongue cancer did not show any improvement as the result of propaganda; the proportion seen first in the third and fourth stage of the affection

was just as high as it had been four, five and six years before. With reference to what Sir Alan Newton had said about country clinics, Dr. Holmes stated that the idea definitely was to provide for diagnosis in suitably equipped hospitals, with experts to use the equipment. A consultative group of experts was provided for the general practitioner and for the patient; the experts would say whether the cancer could or could not be treated efficiently privately or locally, and it would be open to the general practitioner and to the patient to accept or to refuse to be guided by the opinion.

Dr. Zwar, in reply to Dr. Dale's remarks about cancer-phobia, mentioned that at the International Cancer Conference in London in 1928, Wilkie had spoken at some length and had referred to a similar danger, expressing the opinion that the proper avenue for propaganda was through the medical attendant, and that lay journalistic efforts should be regarded as improper.

Medical Societies.

VICTORIAN MEDICAL WOMEN'S SOCIETY.

Honorary Secretary's Report.

THE following is the report of the Honorary Secretary for the year 1936-1937.

During the year 1936-1937 eight meetings have been held, with an average attendance of 23 members.

The most outstanding event of the year was the dinner given in honour of Professor Winifred Cullis, at which forty-eight members were present.

There was a departure from the usual in the clinical pathology evening arranged for us at the Walter and Eliza Hall Institute by Dr. Tewsley and Miss Splatt, B.Sc. A great deal of work had been put into a most fascinating display of modern laboratory methods. At this meeting Dr. Macknight was elected Honorary Treasurer to replace Dr. Hodges, who had sent in her resignation owing to her visit to America with the hockey team.

The excursion took the form of a river picnic to "Fairhaven", but the majority preferred to go by land. After an inspection of the home there was a picnic on the river bank.

The British Medical Association meeting at the Queen Victoria Hospital took the place of our September meeting. Dr. Kincaid, Dr. Barbara Wood and Dr. Alva Boyd and the retiring President, Dr. Lucy Bryce, gave us interesting lectures during the year.

At the September meeting Dr. Jean Greig was nominated again as woman member on the Council of the Victorian Branch of the British Medical Association.

The society has not had to deal with any outstanding business matters, but has sailed along relatively smoothly in the first year of its new constitution. This was formally adopted at the annual meeting, when a number of honorary life members were also unanimously elected in appreciation of their services in the past. Their names are: Lady Leitch, Dr. Janet Lyndsay Greig, Dr. Jean Greig, Dr. Constance Ellis, Dr. Gertrude Halley and Mrs. Eaves. Dr. Clara Stone, another founder, had already been elected an honorary life member.

Office-Bearers.

The committee for 1937-1938 is constituted as follows:

President: Dr. Kate Campbell.
Vice-President: Dr. Florence Cooper.
Honorary Secretary: Dr. Adelaide Gault.
Assistant Honorary Secretary: Dr. Bruce Scott.
Honorary Treasurer: Dr. Ella Macknight.
Committee: Dr. Winifred Kennan, Dr. Lucy Bryce, Dr. Constance Ellis.

Ex Officio:
Vice-President: Dr. Kate Mackay.
Woman Member on the Council of the Victorian Branch of the British Medical Association: Dr. Jean Greig.

Post-Graduate Work.

POST-GRADUATE LECTURES IN MELBOURNE.

THE Melbourne Permanent Post-Graduate Committee announces that two lectures will be delivered at the Medical Society Hall, 426, Albert Street, East Melbourne, by Professor J. C. Meakins, M.D., LL.D. (Edinburgh), F.R.C.P. (Canada), F.R.C.S., F.R.C.P. (Edinburgh), F.R.C.P. (London), Physician-in-Chief of the Royal Victoria Hospital, Montreal, Director of the Department of Medicine, Magill University and Magill University Clinic, late Christison Professor of Therapeutics, University of Edinburgh.

On Monday, May 10, 1937, at 8.15 p.m., the subject will be "Circulatory Collapse: Causes and Cure, with Special Reference to Peripheral Types of Failure".

On Thursday, May 13, 1937, at 8.15 p.m., the subject will be "Systemic Significance of Renal Insufficiency".

An inclusive fee of thirty shillings will be charged. Notice of intention to be present, together with the fee, should be forwarded to the Honorary Secretary, Melbourne Permanent Post-Graduate Committee, 33, Collins Street, Melbourne, C.1.

Correspondence.

CAUSE AND CURE OF CANCER.

SIR: What is done with any extra bricks which are left over when the building of a house is completed? There is no place for them, so they are put aside.

What is done with the extra cells which are left over when the building of a human body is completed? There is no place for them and they cannot be put aside like bricks. They are packed in between cells which have something to do. These extra cells have nothing to do.

A cell which is living and has nothing to do will degenerate. Many of these extra cells will be absorbed, as any foreign body, which is absorbable, will be absorbed. Others of these extra cells will live on, degenerate, and eventually "throw back" to the most primitive form of life, the single cell life (for example the amœba), and assume the habit of the single cell. The single cell individual reproduces by fission or division, that is, the single cell divides into 2, these 2 into 4, to 8, 16, 32, 64 and so on. These increased numbers of cells require room, so a lump appears. This lump increases in size in all directions.

This is cancer.

Cure.—Early diagnosis and excision imperative.

Note.—I feel that radium and X ray therapy have failed to effect a cure for cancer. They inhibit the growth and advance of these cells only. The improvement is temporary.

Yours, etc.,
C. H. ANDERSON,
M.R.C.S. (Eng.), L.R.C.P. (London).

Black Rock,
Victoria,
April 10, 1937.

MENSTRUAL TOWELS.

SIR: Dr. Worrall's letter of March 20 is truly alarming. However, on perusing Dr. Pulvertaft's original article, one finds much to alleviate our fears.

He states: "Tetanus bacilli and Welch's bacilli are consistently present in sanitary towels of cotton wool, or of cellulose wool, also staphylococci, streptococci and *Bacillus coli*.

"Such objects as test tube brushes, the dust of the laboratory floor, were found to contain tetanus spores. . . . In no case were pathogenic organisms found in material sterilized in theatre sterilizers. Autoclaving for 15 minutes at 130° C. killed spore-bearing organisms . . . There is danger that results, such as these here described, may be given grossly exaggerated importance.

"It is not intended to exaggerate the importance of these views . . . Tetanus spores are everywhere. No one has ever contracted or is likely to contract tetanus during the use in menstruation of these towels."

From the above statements of Dr. Pulvertaft, Dr. Worrall and your readers in general may rest assured that the use of ordinary menstrual towels or pads, as they are on the market, is not dangerous and that therefore there is no necessity to demand sterilized towels.

Accouchement sets, on the other hand, are always labelled "sterile"; they are sterile, just as it is self-understood that catgut, so labelled, is sterile.

If, in spite of the above statements, there should be a demand for sterile menstrual towels, manufacturers could easily put such articles on the market, but, of course, at an increased cost.

Yours, etc.,

ALFRED E. FINCKH.

227, Macquarie Street,
April 12, 1937.

MEDICINE AND THE SOCIAL ORDER.

SIR: It is with very great pleasure that I read the article on "Medicine and the Social Order" by Dr. Dark in your issue of the third instant.

It is many years since I first formed the opinion that medicine and the social order, as Dr. Dark terms it, are very vitally related, and as the years have passed I have come more and more firmly to hold that opinion as correct. It is apparent to any practitioner of experience that all medical research will fail in its true goal if the problem of poverty is not faced. Some advance here and there is undoubtedly made and diseases are conquered, but only that new ones appear; really good health is the lot of comparatively few. As Dr. Dark rightly states, medical men are concerned vitally with the health of the people, and therefore concerned vitally with the economic condition of the people. The basic problem for medicine is thus the distribution of the wealth produced by man from nature. It is evident to all that under present conditions this distribution is faulty and uneconomic.

The fact that medical men are beginning to awake to the importance of this factor in the life of the people is probably the biggest advance medicine has made this century. Dr. Dark and others appear to think that the present economic order is passing and will have to pass before we can hope for better things.

I do not believe such a gloomy outlook is necessary; there is no need for any violent change, let alone a complete disruption. All that is necessary is to restore to the people their birthright—that is, equal opportunity to the right to the use of Mother Earth—abolish all special privileges and monopolies, such as the iniquitous sugar embargo, cease the constant clamour for government assistance, and allow mankind to evolve in freedom and justice.

Yours, etc.,

PAUL G. DANE.

110, Collins Street,
Melbourne, C.1,
April 16, 1937.

THE TREATMENT OF GONORRHŒA.

SIR: I have always kept in mind the advice given to some of us when students of Dr. Sinclair Gillies, that if a patient with gonorrhœa were kept in bed for about three weeks and given a diuretic mixture there would be much less trouble with this disease.

In summer gonorrhœa is a different complaint from what it is in winter. In the short winter here I cannot do anything with it. Vaccines are inert, whereas they are most satisfactory in summer.

In winter, if the patient is willing to go to bed, I give an injection of 1,000 millions Commonwealth or "P.D.'s" gonococcal antigen combined. I repeat at five or seven day intervals. The patient remains in bed for fourteen or twenty-one days, taking a diaphoretic and diuretic mixture.

There is a free discharge, which has practically ceased by the time the patient gets up.

The treatment by irrigation is considered by Jausion and others to be not only illogical, but dangerous. An acute gonorrhœa is converted into a chronic condition which no body can see how it will end.

Gonorrhœa as a disease is one matter. Gonorrhœa as an infection another. As we are aware, these organisms are living in many people as apparently harmless saprophytes. We have no satisfactory treatment for their condition.

With the statement of Dr. G. Arbour Stephens (*The British Medical Journal*, 1937, page 540) relative to the difficulty of treating gonorrhœa in tubercular subjects, I am in agreement. The disease seems to smoulder, and I am very sceptical regarding the possibility of cure.

Yours, etc.,

J. MORRIS ROE.

Queen Street,
Brisbane,
April 16, 1937.

The Royal Australasian College of Surgeons.

MEETING OF BOARD OF CENSORS.

THE Royal Australasian College of Surgeons announces that the next meeting of the Australian Board of Censors will be held at the College, Spring Street, Melbourne, in August, 1937. Candidates who desire to present themselves at this meeting should apply to the Censor-in-Chief for permission to do so on or before June 30, 1937. The appropriate forms are available at the College and at the offices of the various State secretaries.

Medical Prizes.

HUNTERIAN SOCIETY: GOLD MEDAL FOR PRACTITIONERS.

ANY registered general practitioner resident within the British Empire is eligible to compete for the Hunterian Society's gold medal for practitioners, and the medal is awarded annually to the writer of the best essay on a subject selected by the society.

Competitors, men or women, must be engaged in general practice, and essays should be sent in by December 31. The essay must be unpublished and original, and be based on the candidate's own observation, but it may contain excerpts from the literature on the subject, provided that reference be made to the articles from which they are taken.

A copy of the rules and any further information can be obtained on application to the Honorary Secretary, Mr. Arthur E. Porritt, 27, Harley Street, London, W.1.

The subject selected for the essay is: 1937, "The Prognosis and Care of Heart Disease in General Practice"; 1938, "The Management of Inoperable Malignant Disease in General Practice".

The 1936 Hunterian Gold Medal for Practitioners was won by Dr. L. J. A. Parr, of Sydney, for his essay on "Rheumatoid Arthritis".

WARNING NOTICE.

MEMBERS of the Victorian Branch are warned against a woman who endeavours to obtain injections of morphine by falsely representing that she is a patient of a consulting physician who has been giving her the drug.

Diary for the Month.

MAY 4.—New South Wales Branch, B.M.A.: Organization and Science Committee.
MAY 5.—Victorian Branch, B.M.A.: Branch.
MAY 5.—Western Australian Branch, B.M.A.: Council.
MAY 6.—South Australian Branch, B.M.A.: Council.
MAY 7.—Queensland Branch, B.M.A.: Branch.
MAY 11.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
MAY 14.—Queensland Branch, B.M.A.: Council.
MAY 18.—New South Wales Branch, B.M.A.: Ethics Committee.
MAY 19.—Western Australian Branch, B.M.A.: Branch.
MAY 20.—New South Wales Branch, B.M.A.: Clinical Meeting.
MAY 25.—New South Wales Branch, B.M.A.: Medical Politics Committee.
MAY 26.—Victorian Branch, B.M.A.: Council.
MAY 27.—New South Wales Branch, B.M.A.: Branch.
MAY 27.—South Australian Branch, B.M.A.: Branch.
MAY 28.—Queensland Branch, B.M.A.: Council.

Medical Appointments.

Dr. S. L. Mainland has been appointed Medical Officer of Health at Narrogin, Western Australia.

* * *

Dr. H. Stubbe has been appointed, pursuant to the provisions of *The Hospitals Act*, 1927, of Western Australia, a member of the Advisory Committee to the Fremantle Hospital.

* * *

Dr. G. S. S. Hayes and Dr. D. W. Johnson have been granted licences authorizing them to sign permissions and certificates for cremation and to grant permission to cremate any human body after death, in accordance with the provisions of *The Cremation Acts*, 1913 *to* 1935, of Queensland.

Medical Appointments Vacant, etc.

For announcements of medical appointments vacant, assistants, *locum tenentes* sought, etc., see "Advertiser", pages xx to xxii.

ANTI-TUBERCULOSIS ASSOCIATION OF NEW SOUTH WALES: Honorary Physician.
CHILDREN'S HOSPITAL (INCORPORATED), PERTH, WESTERN AUSTRALIA: Junior Resident Medical Officers.
DEPARTMENT OF PUBLIC HEALTH, PERTH, WESTERN AUSTRALIA: Resident Medical Officer.
DUNOLLY DISTRICT HOSPITAL, DUNOLLY, VICTORIA: Resident Surgeon.
INSTITUTE OF MEDICAL SCIENCE, ADELAIDE, SOUTH AUSTRALIA: Research Pathologist.
MACKAY HOSPITALS BOARD, MACKAY, QUEENSLAND: Resident Medical Officer.
MANLY DISTRICT HOSPITAL, MANLY, NEW SOUTH WALES: Honorary Officers.
PUBLIC SERVICE BOARD OF SOUTH AUSTRALIA: Assistant Bacteriologist.
REPATRIATION COMMISSION, SYDNEY, NEW SOUTH WALES: Resident Medical Officer.
THE BRISBANE AND SOUTH COAST HOSPITALS BOARD, QUEENSLAND: Honorary Officers.
THE PUBLIC SERVICE BOARD, SYDNEY, NEW SOUTH WALES: Medical Officers.
THE WALLSEND MINING DISTRICT HOSPITAL, WALLSEND, NEW SOUTH WALES: Resident Medical Officer.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment referred to in the following table without having first communicated with the Honorary Secretary of the Branch named in the first column, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

BRANCHES.	APPOINTMENTS.
NEW SOUTH WALES: Honorary Secretary, 135, Macquarie Street, Sydney.	Australian Natives' Association. Ashfield and District United Friendly Societies' Dispensary. Balmain United Friendly Societies' Dispensary. Friendly Society Lodges at Casino. Leichhardt and Petersham United Friendly Societies' Dispensary. Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney. North Sydney Friendly Societies' Dispensary Limited. People's Prudential Assurance Company Limited. Phœnix Mutual Provident Society.
VICTORIAN: Honorary Secretary, Medical Society Hall, East Melbourne.	All Institutes or Medical Dispensaries. Australian Prudential Association, Proprietary, Limited. Mutual National Provident Club. National Provident Association. Hospital or other appointments outside Victoria.
QUEENSLAND: Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17.	Brisbane Associate Friendly Societies' Medical Institute. Proserpine District Hospital. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY Hospital are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.
SOUTH AUSTRALIAN: Secretary, 178, North Terrace, Adelaide.	All Lodge appointments in South Australia. All contract Practice Appointments in South Australia.
WESTERN AUSTRALIAN: Honorary Secretary, 205, Saint George's Terrace, Perth.	All Contract Practice Appointments in Western Australia.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

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